# "TO COMPARE THE EFFECTS OF ORAL MELATONIN VERSUS ORAL PREGABALIN FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ADULT PATIENTS UNDERGOING GENERAL ANESTHESIA. A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL."

**By**

**REG NO. BA0119009**

# Dissertation

**Submitted to the**
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**IN**
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# ENDORSEMENT

This is to certify that the dissertation entitled **"TO COMPARE THE EFFECTS OF ORAL MELATONIN VERSUS ORAL PREGABALIN FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ADULT PATIENTS UNDERGOING GENERAL ANESTHESIA. A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL."** is a bonafide research work done by **REG NO: BA0119009** Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belagavi – 590 010.

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## ACCEPTANCE LETTER

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## LIST OF ABBREVIATIONS USED

| | | | |
|---|---|---|---|
| 1. | HR | = | Heart Rate |
| 2. | SBP | = | Systolic Blood Pressure |
| 3. | DBP | = | Diastolic Blood Pressure |
| 4. | MAP | = | Mean Arterial Pressure |
| 5. | CNS | = | Central Nervous System |
| 6. | ICU | = | Intensive Care Unit |
| 7. | GABA | = | Gamma-Aminobutyric Acid |
| 8. | $CMRO_2$ | = | Cerebral Metabolic Rate for Oxygen |
| 9. | ICP | = | Intracranial Pressure. |
| 10. | SVR | = | systemic vascular resistance |
| 11. | ACTH | = | adrenocorticotropic hormone |
| 12. | BIS | = | Bispectral Index |
| 13. | CHF | = | Congestive Heart Failure |
| 14. | ASA | = | American Society of Anaesthesiologists |
| 15. | $N_2O$ | = | Nitrous Oxide |
| 16. | yrs | = | years |
| 17. | Kg | = | kilogram |
| 18. | Mg | = | milligrams |
| 19. | cms | = | centimeters |
| 20. | S.D | = | Standard Deviation |
| 21. | CO | = | Cardiac Output |
| 22. | MT | = | Melatonin |
| 23. | MT-1 | = | Melatonin 1 Receptor |

| | | | |
|---|---|---|---|
| 24. | MT-2 | = | Melatonin 2 Receptor |
| 25. | Inj. | = | injection |
| 26. | IL-2 | = | Interleukin 2 |
| 27. | NF-KB | = | Nuclear Factor kappa-light-chain-enhancer of activated B cells |
| 28. | BP | = | Blood Pressure |
| 29. | I.V | = | Intravenous |
| 30. | MAC | = | Minimum alveolar concentration |
| 31. | RCT | = | Randomized control trial |
| 32. | α | = | Alpha |
| 33. | β | = | Beta |
| 34. | SPO2 | = | Saturation percentage of oxygen |
| 35. | MPG | = | Mallampati Grading |
| 36. | CO2 | = | Carbondioxide |
| 37. | O2 | = | Oxygen |
| 38. | N2O | = | Nitrous Oxide |
| 39. | BMI | = | Body mass index |
| 40. | BMR | = | Basal metabolic rate |
| 41. | CYP | = | Cytochrome P |
| 42. | µg / mcg | = | Micrograms |
| 43. | mg | = | Milligrams |
| 44. | Kg | = | Kilogram |
| 45. | ml | = | Milliliters |
| 46. | & | = | And |

# ABSTRACT

Background: Endotracheal intubation is one of the standard procedures to secure an airway. Following laryngoscopy, there is a hemodynamic response because of the noxious stimulus which results in reflex sympathetic stimulation. This results in haemodynamic changes. These changes undesirable and has detrimental effects on patients with diseases like coronary artery diseases, vascular anomaly & aneurysm. To attenuate hemodynamic changes various drugs & techniques are used. Recently some studies show evidence of using agents like oral Melatonin (MT) and oral Pregabalin are effective in attenuating haemodynamic response. The present prospective randomized study is comparing efficacy of both the drugs.

**Methods: -** After obtaining approval from ethical committee,60 patients were recruited who were belonging to ASA Grade 1&2, aged between 18-60years and randomized into 2 groups. These patients received two tablets of either oral melatonin(6mg) group A or oral pregabalin (150mg) group B 120minutes prior to laryngoscopy and intubation. The haemodynamic changes were noted at baseline, at induction & post-intubation at 1min,3min,5min,10min respectively and tabulated.

**Results:** The haemodynamic changes were attenuated effectively by both the drugs. Melatonin had significant more attenuation of Diastolic blood pressure and mean arterial pressure when compared to pregabalin.

**Conclusion:** The present study aids in concluding that premedicating 120minutes prior to intubation with oral melatonin(6mg) or pregabalin(150mg) would attenuate haemodynamic response to laryngoscopy and intubation. However further research is required.



**Keywords:** Haemodynamic stressor response, melatonin, pregabalin

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# INTRODUCTION

Endotracheal intubation is one of the standard procedures to secure an airway. It aids in providing a conduit for delivery of anaesthetized gases providing positive pressure ventilation while maintaining airway pressures and helping in protecting the airway from aspiration of gastric contents. Laryngoscopy is commonly used technique for intubation. Following laryngoscopy, there is a hemodynamic response because of the noxious stimulus which results in reflex sympathetic stimulation which is caused by epi-pharyngeal and laryngo-pharyngeal stimulation[1]. Due to this, there is an increase in plasma concentrations of nor-epinephrine & other catecholamines which results in tachycardia, hypertension, and arrhythmias[2]. These haemodynamic changes that occur due to laryngoscopy and intubation may cause a change in the balance of myocardial oxygen demand & supply and can increase the chances for myocardial ischemia in patients with known ischemic heart diseases. It is undesirable and has detrimental effects on patients with diseases like coronary artery diseases, vascular anomaly, aneurysm, etc.

To avoid such complications and to attenuate hemodynamic changes during laryngoscopy & intubation various agents like fentanyl[3], lignocaine[5], beta-blockers(esmolol)[3], calcium channel blockers or interventions like maintaining good depth of anaesthesia, use of nerve blocks[4] have been found to reduce the haemodynamic response.

Recently some studies show evidence of using agents like oral Melatonin (MT)[6] and oral Pregabalin[7] are effective in attenuating haemodynamic response.

Pregabalin which is a gaba-pentinoid molecule. It is a structural representation of (S)-3 aminomethyl-5-methylhexanoic acid. It is similar to gamma-aminobutyric acid (GABA) which is an inhibitory neurotransmitter and its function is not similar. Its mechanism of

action is by reducing the synthesis of neurotransmitter glutamate. It has anxiolytic, analgesic and anticonvulsant activity. It is effective in inhibiting nociceptive pain due to surgery and attenuation of stress response due to laryngoscopy and intubation and reduces the release of catecholamines[8].

Melatonin (MT) is a ubiquitous molecule. It is secreted by the pineal gland at night. It is a sleep-promoting molecule with clock phase resetting functions in humans. The mechanism of melatonin is complex. The blood pressure-decreasing mechanism is because of melatonin binding to receptors MT-1 and MT-2 in the blood vessels which also interfere with vascular response to catecholamines[9]. The sedative action is mostly because of melatonin molecule binding at GABA‑A receptor[5].

In this study, we plan to compare the efficacy of oral melatonin and pregabalin to attenuate the haemodynamic response to laryngoscopy and intubation.

# AIMS AND OBJECTIVES

**PRIMARY OBJECTIVE:**

To compare the efficacy of oral melatonin versus oral pregabalin in attenuating haemodynamic response to laryngoscopy and intubation in adult patients.

**SECONDARY OBJECTIVE:**

To study the side effects of oral melatonin and oral pregabalin if any.

# REVIEW OF LITERATURE

In a study conducted by **Gupta P[6]**, 60 patients with ASA status Grade I and II posted for non-emergency surgeries under general anaesthesia(GA) have been selected & divided into 2 equal groups; Group C (control) & Group M (melatonin) where they were orally given placebo & tablet melatonin 6 mg, 120 mins prior surgery. The systolic (SBP), diastolic (DBP), mean arterial pressures (MAP) and Heart rate (HR) were recorded prior to surgery, laryngoscopy and intubation, and also at 1, 3, 5, and 10 minutes(min). A significant rise in HR & blood pressure (BP) at the time of laryngoscopy was observed which continued till 10mins post intubation. In the melatonin group it had been observed that there was an irrelevant rise in HR at laryngoscopy & intubation, which also reduced within 1 min after intubation.

In a study conducted by **Serenella Arangino[10]**, it was found that when 1mg melatonin given orally in assessment to placebo was able to decrease the haemodynamic pressures & vascular-activity to catecholamines levels. Melatonin significantly decreased blood pressure and levels of catecholamines within 90 minutes. Present data indicate that melatonin may blunt the activity of the cardiovascular system.

**Puja Thapa[11]** conducted a doubled blinded randomised study in which 50 patients with treated hypertension were enrolled and divided into 2 equal groups

One group received 75mg of pregabalin capsule and other group received multivitamin capsule 60 minutes prior to induction of general anaesthesia. It was concluded that oral dose of 75mg of pregabalin was efficient and significantly reduced haemodynamic response to laryngoscopy and intubation.

In a study conducted by **Samarkandi A[12],** where seven groups of children were arbitrarily allocated to receive premedication. They were given Midazolam of (0.1, 0.25 or 0.5 mg/kg) orally, or melatonin (0.1, 0.25 or 0.5 mg/kg) orally where each group was added with 15 mg/kg acetaminophen. It was found that melatonin has same effect as midazolam in reducing anxiety in children. It also aids with enhanced recovery & a reduced incidence of sleep associated disorder which is seen postoperatively.

In a study done by **Madhuri S Kurdi[13],** 2 doses of oral melatonin was compared with oral midazolam in children. They compared sedation, cognition & parental separation anxiety. This was a prospective double blinded study directed to 100 children aged 5-15 years. They were randomized into 4 groups of 25 each (A, B, C, D). Each group received oral melatonin tablet 0.5 mg/kg, 0.75 mg/kg, oral midazolam 0.5 mg/kg or placebo 45-60 mins respectively as per their assigned group prior to induction. They concluded that Oral melatonin 0.5 mg/kg & 0.75 mg/kg in children reduced anxiety pre-operatively without reducing the cognitive & psychomotor functions for which the most effective dose is 0.75 mg/kg.

A randomized controlled study conducted by **Rastogi B[14],** used oral pregabalin in different doses as a pre-medication to reduce haemodynamic response to laryngoscopy. A total of 90 adults aged 24-56 years of ASA grade I and II were randomized into 3 groups. Oral placebo was given to Group I patients, Group II patients received oral pregabalin75mg & Group III patients were given oral pregabalin 150mg, 60 minutes prior to induction. The groups were evaluated for perioperative pressor changes and sedation, before induction followed by laryngoscopy and side-effects.it was

concluded that oral pregabalin premedication has sedation effect on the patients.it was also seen that the haemodynamic response for intubation was reduced.

In a randomized double blinded study done by **Dheer Singh[15],** sixty patients of ASA physical grade I & II, posted for planned non-emergency laparoscopic cholecystectomy. They were arbitrarily assigned into 2 groups where either of the group would receive oral placebo or pregabalin 150mg, one hour before anaesthesia induction. Anxiety was assessed by visual analog scale (VAS) before and 1 hour after receiving the drug. HR, SBP, DBP & MAP was noted prior, 1hour post drug administration & 2, 4, 6, 8, and 10 mins post-intubation. It was established that pregabalin is highly efficacious in reducing the anxiety preoperatively & haemodynamic pressor response to laryngoscopy and intubation.

In a double-blinded study done by **Ayya Syama Sundar[16]**, evaluation was done by dividing 60 patients who were listed for elective off-pump coronary artery bypass surgery into 2 equal groups. In the control group, patients received placebo drug. while in other group, they were given pregabalin 150mg capsules per orally 60mins prior to surgery. These patients were assessed for hemodynamic changes prior to surgery, after induction, 1min, 3min & 5 mins post intubation. It shows that an oral administration of pregabalin at a dose of 150mg when given 60mins prior to surgery reduces the haemodynamic stimulus to laryngoscopy & tracheal intubation.

**Geeta Bhandari[17]** conducted a double blinded study on 60 patients of ASA status I & II who were planned for elective surgical procedures under GA. They were arbitrarily allotted into 2 equal groups where they received 150mg of oral pregabalin or placebo

60mins prior to surgery. Haemodynamic responses were recorded at preoperative laryngoscopy, and 0 minute,1 minute,3 minute,5 minute and 10 minutes post-intubation. It was concluded that administration of 150mg oral Pregabalin as a premedicant 1hour before to surgery decreases the haemodynamic response that is associated with the procedure of laryngoscopy & endotracheal intubation.

In a study conducted by **Gupta K[18]** 80 adults of ASA grade I and II aged between 24-54 years were recruited and given oral pregabalin 150 mg or placebo capsule 60-75 min prior to surgery. These two groups were evaluated for preoperative sedation and haemodynamic changes before and after the induction and 1, 3, 5, and 10 min after laryngoscopy and post-intubation. It was found that oral administration of pregabalin as a premedication is effective which aids in providing sedation and also analgesia with effective reduction in hemodynamic pressor response.

**Borazan H[19]** conducted a study on 52 ASA I&II patients who were planned for prostatectomy electively were included. They were randomized into 2 groups. Oral placebo was given to one group of patients whereas the other group received 6mg of melatonin the night prior & 60min before surgery. It was found that when melatonin was administered prior to surgery it has aided in decreasing pain scores & also decreased tramadol usage and increased the quality of sleep, sedation scores, & promoted analgesic efficacy during post-operative period.

In a study conducted by **Bu¨lent Ku¨cu¨kakin[20],** in patients who were listed for aortic aneurysm surgery. 6 patients received 10mg of Inj. melatonin IV during the intraoperative period & 10mg melatonin tablets orally for 3 nights post-surgery. Haemodynamic parameters during & post-surgery were monitored in all patients. It was

noted that melatonin administration did not change hemodynamic parameters during surgery, but oxidative stress parameters decreased significantly.

In a study conducted by **AHMED A**[21] where patients were randomized into 3 groups and group 1 received placebo, group 2 received 6mg of melatonin, group 3 received 9mg of melatonin. It was concluded that preoperative administration of oral melatonin decreased haemodynamic stressor response.

In a study conducted by **Naguib M**[22] where 200 patients were randomized into 2 groups and patients of group 1 received melatonin at dose of (0.2mg/kg) and group 2 received placebo. It was concluded that the group which received melatonin as a premedication decreased the dose of thiopentone & propofol for induction.

**Turkistani A**[23] conducted a study where 45 patients were randomized into 3 groups and group(M3) was given 3mg of oral melatonin, group(M5) received 5mg of oral melatonin & group (P) received placebo. It was concluded that the required dosage of propofol to get a BIS score of 45 was significantly reduced in melatonin groups.

# BASIC SCIENCE

## ANATOMY OF THE AIRWAY

Airway is the channel through which air passes in & out the lung during respiration. The airway begins from the nose & ends at bronchioles. Airway is divided into upper airway and lower airway. Upper airway begins from the nose and extends to the glottis & lower airway begins from the glottis which includes trachea, bronchi its sub-divisions.

## NOSE

Nose begins from nares posteriorly to the naso-pharynx for 10 to 14 centimetres & two nasal fossae are separated in the midline through the septum which is formed by cartilages and bony parts. It aids in filtration, respiration, humidification of gas, olfaction and it aids in phonation as well.

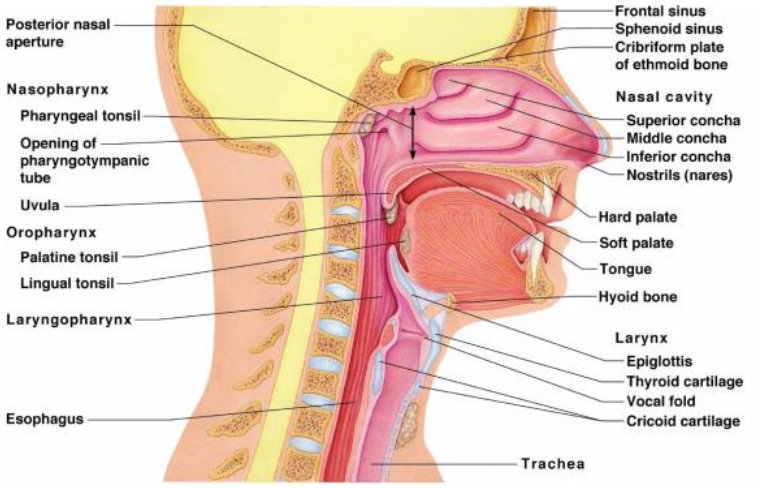



**Fig 1: Sagittal section of upper respiratory tract**

## PHARYNX

Pharynx begins from base of skull it measures at 12- 15 centimetres. It ends anteriorly to cricoid cartilage and posteriorly to inferior border of 6$^{th}$ cervical vertebra.

**LARYNX**

Larynx is made of cartilage. It is present opposite to the cervical vertebrae where it begins from 3rd and extends to 6th in adults.

It is made of cartilage, ligament & muscles where every structure has an important role.

The larynx is made of 9 cartilages, 3 paired & 3 unpaired cartilages.

There are 3 unpaired cartilages which are

1. Thyroid

2. cricoid

3. epiglottis.

There are 3 paired cartilages

1. arytenoids,

2. corniculate

3. cuneiform.

Laryngeal cavity begins from epiglottis and extends to sub glottis.

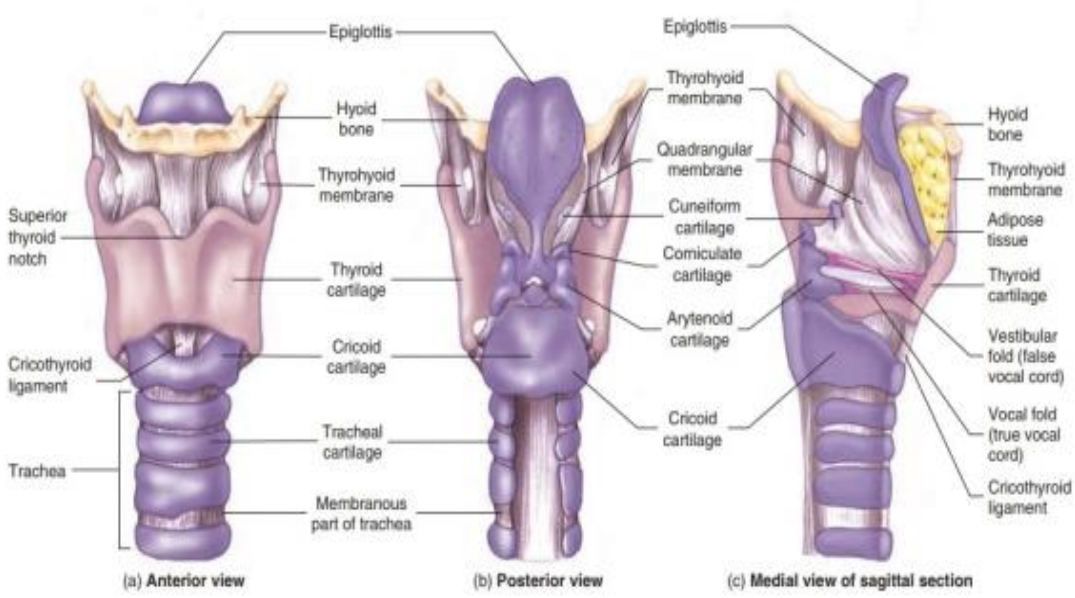



**Fig 2: Anterior, posterior and sagittal view of larynx**

## NERVE INNERVATIONS

### Pharynx

The pharynx is innervated by cranial nerves $7^{th}$, $9^{th}$, $10^{th}$, and $12^{th}$. The motor & sensory innervation to most of the pharynx other than nasopharynx is innervated by the pharyngeal plexus. Pharyngeal plexus, are present above the middle pharyngeal constrictor which is made by:

1. The Pharyngeal branches which arise from the glossopharyngeal nerve i.e. $9^{th}$ cranial nerve.
2. The Pharyngeal branches which arise from the vagus nerve i.e. $10^{th}$ cranial nerve.
3. Branches which arise from the external laryngeal nerve
4. There are Sympathetic nerve fibres which arise from the superior cervical ganglion.

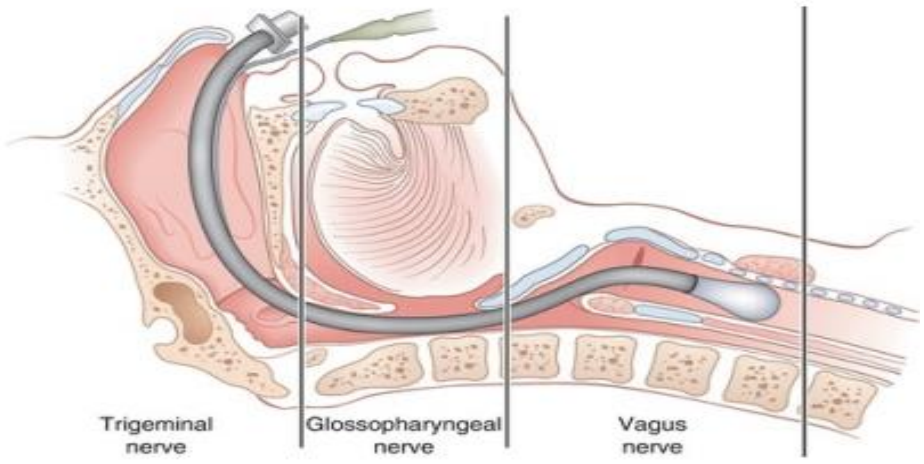



**Fig 3: Airway and its nerve innervations**

### Sensory Innervations:

Pharynx is supplied with sensory innervation from the glossopharyngeal nerve. The superior & anterior part of naso-pharynx is supplied by the maxillary nerve whereas the inferior aspect of the laryngo-pharynx is supplied by internal branch of the vagus nerve.

Motor Innervations:

In pharynx all the muscles are supplied by the vagus nerve, apart from the stylopharyngeus muscle, which is supplied by the glossopharyngeal nerve.

**Larynx:**

Larynx is innervated by the vagus 10$^{th}$ cranial nerve where it gives branches as

1. Superior laryngeal nerve branch.

2. Recurrent laryngeal nerve branch.

**Superior laryngeal nerve:**

The internal division of superior laryngeal nerve supplies the epiglottis, the base of tongue, supra-glottic mucosa, thyro-epiglottic joint & crico-thyroid joint.

The external division of superior laryngeal nerve gives sensory innervations to anterior subglottic mucosa and motor innervations to crico-thyroid muscle which is adductor, tensor.

The Recurrent laryngeal nerve provides sensory supply to the sub-glottic mucosa & muscle spindles. It also provides motor supply to thyro-arytenoid, lateral crico-arytenoid, inter arytenoids & posterior crico-arytenoid.

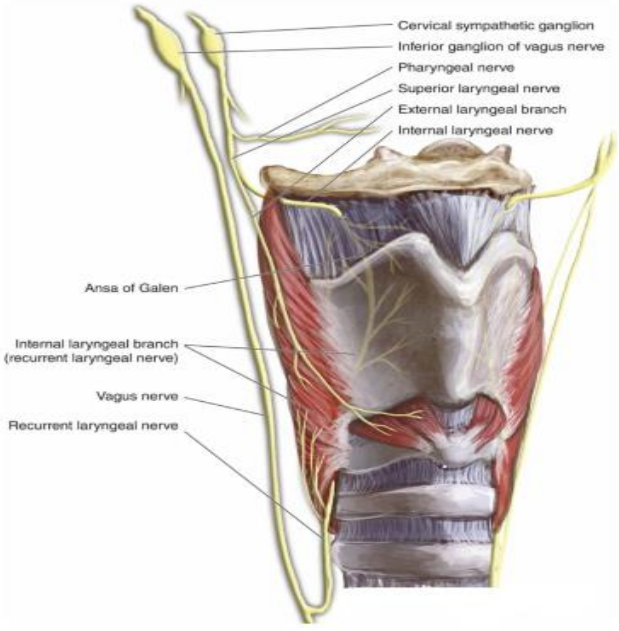



**Fig 4: Larynx and its nerve innervations**

## THE AIRWAY REFLEXES

The upper airway reflexes are of importance. There are numerous types of nerve innervations that are present within & below the epithelium of the upper airway. The afferent nerve endings will initiate reflex action.

Upper airway reflexes can be response to stimulus such as sneezing, swallowing, coughing, expiration reflex & negative pressure reflex. If the receptors of the upper respiratory tract are irritated it will results in a reflex motor response.

Receptors of the respiratory tract are:

1. The slowly adapting stretch receptors responsible for the Hering-Breuer reflex,
2. The rapidly adapting irritant receptors when activated because of touch, chemical stimuli, dust & cold air.

The rapidly adapting receptors are accountable for the cough reflex. There are laryngeal afferent neurons which are present in the epiglottis. Mechanical stimuli are found to produce more profound effect when compared other stimuli like a light touch that only passes over few receptive fields.

There are sensory units which made by free nerve endings which are present among the mucosal cells in the epithelial layer of airway. These sensory units are seen to be chiefly plentiful along the arytenoid cartilage & they are also located on the mucosal layer of the laryngeal side of epiglottis.

The superior laryngeal nerve has numerous small diameter myelinated fibres which are of group III, A delta or B sensory fibres, these transmit the afferent stimuli from rapidly adapting receptors & the epiglottis.

The recurrent laryngeal nerve has the sensory fibres, which are mostly given from rapidly adapting receptors which get activated by a light touch and these receptors are in abundant number at the anterior & posterior side of the inferior surface of the vocal

cords. When these get stimulated the receptors produce in vocal cord movement. The afferent fibres in the laryngeal nerves are represented centrally to the tractus-solitarius nucleus, specifically in the caudal and posterior regions.

Laryngeal closure is very intricate muscular occurrence where it involves the action of multiple muscles that have abductor effect when they get activated. The activation of the laryngeal muscles due to the stimulus from internal branch of the superior laryngeal nerve would result in reflex laryngeal closure & is a more forceful closure than closure which occurs from stimulating recurrent laryngeal nerve, where laryngeal muscles act directly and are less coordinated.

## RESPONSE TO INTUBATION

Laryngoscopy & intubation activates various physiological and pathophysiological reflexes. The stimulation of afferent receptors in the posterior pharynx is innervated by the glossopharyngeal and vagus nerves.

The various systems of body which include central nervous system, cardiovascular system, and respiratory system react to these afferent stimuli, and it may have detrimental effect selected patients.

Stimulation of the autonomic nervous system will increase in the heart rate and blood pressure, & also stimulation of the upper and lower respiratory tract result in more airway resistance, which might result in adverse events in a patient with comorbidities.

The detailed mechanism of the intubation response is indefinable. It is been well-known that there are both a sympathetic & parasympathetic pathways.

The sympathetic pathway is polysynaptic where glossopharyngeal nerve & vagus nerve forms the afferent arc of sympathetic nervous system through the brain stem & spinal cord[26]. This results in an autonomic response near the efferent side which increase and causes rapid firing of the cardio-accelerator fibres & release mediators which include nor-epinephrine, epinephrine & vasopressin.

Airway manipulation stimulates central nervous system by increasing cerebral metabolic oxygen demand & cerebral blood flow. If there is a decrease in intracranial compliance, there will be an increase in CBF which may increase the ICP more. This response is vital in conditions where there is loss of auto-regulation which changes in the blood flow to the brain and becomes pressure-passive which results in increased blood pressure which in turn result in raised ICP.

In 1951 it was proved that when patient is under lighter planes of anaesthesia direct laryngoscopy and tracheal intubation would result in producing raised Blood pressure & heart rate[26].

The Cardiovascular system response is due to secretion of epinephrine from adrenal medulla, norepinephrine which is released from adrenergic nerve terminal & also activation of Renin-Angiotensin-Aldosterone system. In children it is believed to be a monosynaptic reflex stimulating vagus & sinoatrial node, which result in bradycardia.

Adults have a polysynaptic incident which prevails by impulses movement afferently by the $9^{th}$ & $10^{th}$ cranial nerves to the brain stem and spinal cord. The efferent sympathetic response is due to norepinephrine, epinephrine release from adrenergic nerve terminals & activation of the renin– angiotensin system which leads to tachycardia & hypertension. The respiratory system response is in 3 important pathways to laryngoscopy & intubation by activation of the upper airway reflex which leads to laryngospasm; coughing; and bronchospasm. This also result in increased airway resistance.

**Limiting haemodynamic stressor response by using technical methods:**

Limiting of pressor response by applying gentle cricoid pressure, performing laryngoscopy using Macintosh or McCoy blade compared to Miller blade[27] & Use of Laryngeal Mask Airway and not ETT[32] which usually result in decreased hemodynamic disturbances.

1. **Use of topical Anaesthesia to reduce the stressor response**:

Topical anaesthesia of 10% lignocaine spray[28], use of nerve blocks of superior laryngeal nerve, glossopharyngeal nerve and trans tracheal blocks will minimize stressor response.

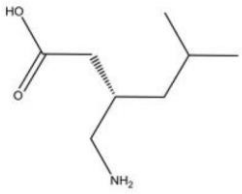
2. **Inhalational Anaesthetics and its use in limiting stressor response:**

Use of inhalation agents at MAC of 2.5 to 3 will result reduced hemodynamic response to intubation[29].

3. **Use of intravenous agents to limit haemodynamic response**:

i. Use of opioids like Fentanyl, Alfentanil & Remifentanil[30].
ii. Use of local anaesthetics 2% lidocaine (Loxicard).
iii. Use of β adrenergic receptor antagonist & Calcium channel blockers like Esmolol, Labetalol, verapamil, nifedipine & nimodipine.
iv. Use of vasodilators& α2 agonist like Nitroglycerine & Dexmedetomidine[33].

## PREGABALIN




**Pregabalin**
(S)-3-(Aminomethyl)-5-methylhexanoic acid

FIG 5: Chemical formula of pregabalin

Pregabalin, or S-(+)-3-isobutylgaba, is a lipophilic equivalent of GABA replaced at the 3-position to aid diffusion across the blood–brain barrier.

Though pregabalin is structurally correlated to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically. It does not have affinity for receptor sites or alter responses associated with the action of several common drugs for treating seizures or pain.

**Mechanism Of Action**

It attaches to alpha2-beta subunit of pre-synaptic, voltage-dependent $ca^{2+}$ channels[24] that are located at the central and peripheral nervous system. It also decreases the release of other neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, and substance P. It is not active at GABA A and GABA B receptors.

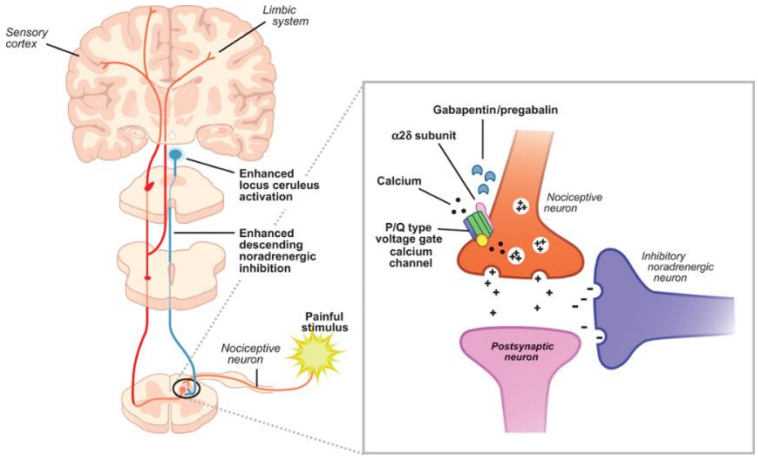



**Fig 6: Mechanism of action of pregabalin**

## PHARMACOKINETICS

### Absorption

Pregabalin is promptly & widely absorbed after oral dosing in the fasting state, with maximal plasma concentrations occurring 60-90minutes after single dose, and steady state being accomplished within 24–48 h after repeated administration.

### Half-Life

It has a half- life of 6.3 hours

### Metabolism And Excretion

It has insignificant metabolism in humans and is excreted unchanged by the kidneys. It is not bound to any of plasma proteins.

## PHARMACODYNAMICS

It decreases the sensitivity of dorsal horn neurons which also has effect in reducing the chronic pain. It quickly crosses the blood brain barrier it decreases the interaction between the nerves and this results in effective antiepileptic action.

### Routes Of Administration

Oral tablets: dose:50-600 mg/day

### Side effects

Dizziness, dry mouth, muscle pain and weakness.

### Contraindication:

Nil, except hypersensitivity to the drug.

**MELATONIN**

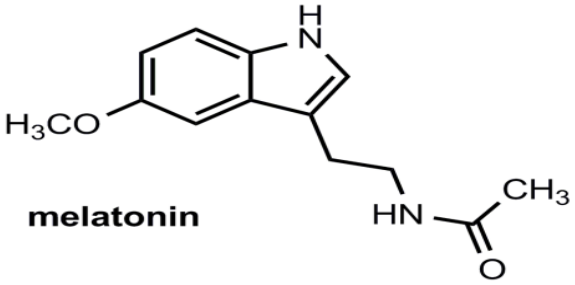



**Fig 7: Chemical formula of melatonin**.

Melatonin was discovered in 1958. The Molecular formula is C13H16N2O2. The Molecular weight is 232.28 g/mol.

Melatonin is a natural substance which is present in all organisms. It is secreted by the pineal gland. The secretion is usually increased during night and reduced during day. It is produced from tryptophan in peripheral tissues & other organs.

**PHARMACOKINETICS:**

Melatonin is quickly distributed and eliminated after intravenous administration. After administering orally, the plasma concentration is peaked at 60-120 minutes and is then eliminated. Melatonin has a half -life of 55 to 90 minutes, where 90% of orally administered melatonin is eliminated through the liver, a small amount is excreted in urine, & a small amount is found in saliva. The bioavailability of melatonin is between 10 and 50%.

Melatonin is metabolised by liver using cytochrome P450 enzyme CYP1A2 to 6-hydroxymelatonin. These metabolites are conjugated by sulphuric acid or glucuronic acid and help in excretion by urine. 5% of melatonin is eliminated in the urine as the unchanged drug. Metabolites formed due to the reaction of melatonin with a free radical which include cyclic 3-hydroxymelatonin, N-acetyl-N2-formyl-5-methoxy kynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK).

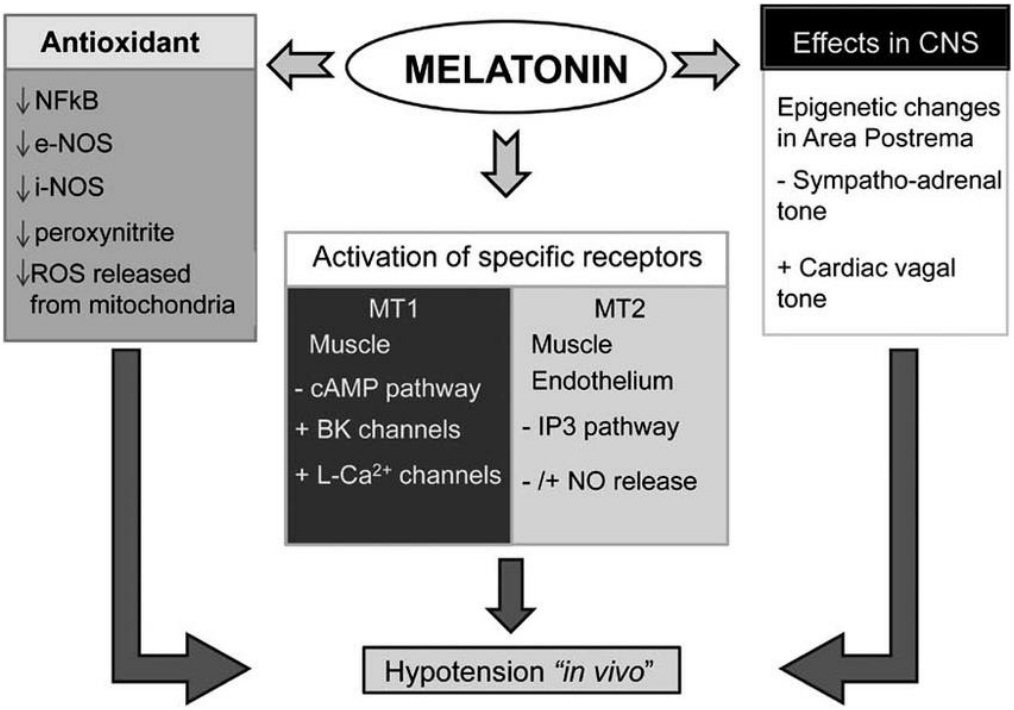



**Fig 8: Mechanism of action of melatonin**

**PHARMACODYNAMICS**

When small amounts of melatonin about 0.3 mg given several hours prior to sleep it aids in shifting the circadian clock prior which observed in the phase response curve for melatonin in humans which result in promoting sleep onset & morning awakening. Melatonin is an agonist of melatonin receptor 1(MT1) which has picomolar binding affinity & melatonin receptor 2(MT2) which has nanomolar binding affinity. These both receptors belong to the class of G-protein coupled receptors (GPCRs). These receptors 1 and 2 are both $G_{i/o}$ - coupled GPCRs, but MT1 is Gq- coupled. Melatonin has high-capacity free radical scavenging within mitochondria & also promotes the manifestation of anti-oxidant enzymes such as superoxide dismutase, glutathione reductase, & catalase through melatonin receptors.

**Melatonin and its aid to anaesthesiologist:**

**1.Melatonin and its aid in sleep induction and maintenance:**

Melatonin is used for both initiation and maintenance of sleep and also has hypnotic effects. It improves sleep onset, duration and quality. This effect is because of the activation of the MT1 and MT2 receptors. It also suppresses neuronal activity through which it aids in regulation of sleep. There are central effects of melatonin which involves change in the activity of GABA receptor which facilitates GABA transmission. There are no negative effects like addiction& dependence which are seen with Benzodiazepines.

**2. Analgesic effects of melatonin**

Melatonin has analgesic effects in a dose-dependent method in studies. The physiological mechanism of its analgesic effect is yet to be clarified. It could be related to Gi-coupled melatonin receptors, GABA-B receptors or Gi- coupled opioid μ receptors. It acts by augmenting GABA system & morphine anti-nociception, also inhibits glycine effect & enhances GABA induced action. It activates MT2 receptors in the dorsal horn of spinal cord & also improve the levels of β-endorphins & the anti-nociception induced by delta opioid receptor agonists.

**3. Melatonin its Anti-Inflammatory effects**

It has shown anti-corticoid effect in studies which has immune improving effect. It has modulatory influence on the NO synthetase (NOS)[25] and cytokine production in inflammatory and oncostatic processes. It combats various bacterial and viral infections.

The mechanisms for melatonin's anti-inflammatory effects include

A. Modulation of the pineal and pituitary / adrenal axis activity

B. Lowering of corticoid levels by releasing vasotocin

C. Inhibition of COX2 enzyme and iNOS enzyme

**4. Melatonin and its anti-oxidative effect**

It is a powerful antioxidant. It decreases the damage induced by free radicals & improves the activity of various antioxidant enzymes like catalase, glutathione reductase and glutathione S transferase.

**5. Melatonin and its chrono biotic property**:

It is an important regulator of the body circadian rhythm, anaesthesia and surgery disturbs the onset of nocturnal melatonin secretion.

**6. Anti-Hypertensive Property**:

It has a mild hypotensive effect as it binds to melatonin receptors in the blood vessels & interact with the vascular response to catecholamines[25]. It also interrupts with the peripheral & central autonomic system which results in a reduction in adrenergic outflow & catecholamine levels. It also induces relaxation of the arterial wall smooth muscle by increasing nitric oxide levels[35].

**7. Ocular hypotensive effect of melatonin:**

Melatonin has ocular hypotensive effect[34]. It may have a complex undefined role in aqueous humour formation. Melatonin receptors (M2 and M3) were recognized in the ciliary body tissues in animals.

**8. Immunological effects of Melatonin**

A. Activation of NF-kB, inhibition of neutrophil infiltration

B. Enhancement of thymocyte proliferation and IL2 production.

**Routes of administration**

Oral tablets:-dose 3mg/10mg tablets

**Side effect**

Headache, Dizziness, Nausea &Drowsiness

**Contraindications**: NIL

# METHODOLOGY

The present study is titled **"TO COMPARE THE EFFECTS OF ORAL MELATONIN VERSUS ORAL PREGABALIN FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ADULT PATIENTS UNDERGOING GENERAL ANESTHESIA. A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL."** Was undertaken in the "Department of Anaesthesiology, KLE'S Dr. Prabhakar Kore Hospital, Belagavi during the period of January 2020 to March 2021."

**Source of data**

Participants who are aged between 18 to 60 yrs. of both genders who belong to the ASA physical grade I & II and were undergoing planned surgical procedure under GA with tracheal intubation at "KLE's Dr. Prabhakar Kore Charitable Hospital And Medical Research Centre, Nehru Nagar, Belagavi -10_during the period from January 2020 to March 2021."

**Study design:** A one year Randomized Control Trial.

**Study duration**:

January 2020 - March 2021

**Selection Criteria**

**Inclusion Criteria**:

- Patient who provides consent.
- ASA physical grade I & II.
- Aged between 18-60 years.
- Patients undergoing elective surgeries under GA with endotracheal intubations.

**Exclusion Criteria**:

- Hypertensive patients who are ASA grade 3 and 4
- ASA grade 3 and 4
- Patients allergic to study drug
- Patients with difficult airway
- Patients with known body weight >100 kg, parturient, obese or breast-feeding females

**Sample size:**

Total sample-60

Group A - 30

Group B – 30

**Sample size calculation:**

‘‘The minimum sample size formula based on mean and standard deviation is

$$n = \frac{(z_\alpha + z_\beta)^2 (s_1^2 + s_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

where $z_\alpha$ is linked with the level of significance and $z_\beta$ is linked with the power of the test. For 5% level of the significance $z_\alpha$ =1.96 and $z_\beta$ =0.84 for 80% power of the test.

REF: Gupta P, Jethava D, Choudhary R, Jethava DD. Role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation.

$\bar{X}_1$ is the mean of the first group (89.87) and $\bar{X}_2$ is the mean of the second group (79.00).

$s_1$ is the standard deviation of the first group (11.65) and $s_2$ is the deviation of the second group (10.02).

With these values the sample size obtained is 16.

There will be two groups having with minimum – cases in each group.

To make the study more confirmative, the sample size will be raised to 30

There will two groups with size 30 each.

**Methodology:**

After obtaining the clearance from ethical board & written informed consent, 60 patients who are to undergo elective surgical procedure under GA with endotracheal intubation were included in the study.

After having met inclusion & exclusion criteria, computer generated randomization was used to randomize patients into either of the two groups.

**Group A:** Patients were given two tablets 3mg each of oral melatonin (6mg) 120 minutes prior to surgery.

**Group B**: Patients were given two tablets each of 75mg of pregabalin (150mg) 120 minutes prior to surgery.

Pre-anaesthetic evaluation was done on day before surgery. Detailed medical history was elicited and detailed physical examination was carried out. Preoperatively investigations like CBC, RBS and Sr. Creatinine were done. ECG and CXR were done if patient was more than 40 years of age.

On the procedural day, 8 hours nil per oral status was ensured in all patients prior to surgery,18G I.V line was secured in the pre-operative recovery room and I.V fluids were started. Patients were randomly assigned into two groups based on computer generated. Patients from each group received a coded enteral preparation which contained two tablets 3mg each melatonin total of (6mg) or pregabalin two tablets 75mg each total of 150mg. Approximately 120 mins prior to the expected induction time, Group A received melatonin (6mg) whereas Group B had received 150mg pregabalin by the anaesthetic staff with small sips of water.

In the operating room (OR), vital monitors such as the BP, ECG, pulse oximetry were attached. BP: systolic pressure, diastolic pressure & mean arterial pressure was obtained by non-invasive brachial oscillometry. HR was documented from the lead II of ECG. Baseline readings of the vitals were taken 5 mins after the patient was settled on the operating table. Patient were pre-oxygenated for 5 minutes with 100% oxygen. I.V. Glycopyrrolate 0.004mg/kg, Midazolam 0.05mg/kg, fentanyl 2 μg/kg was given then induction was proceeded with I.V. Thiopentone 5mg/kg followed by the administration of I.V. succinylcholine 2mg/kg to ease tracheal intubation. Ventilation was manually controlled by Bain's circuit with 100% oxygen as soon as the thiopentone was administered. BP (systolic, diastolic & mean) & HR were recorded after the patient was induced and before laryngoscopy was conducted. Laryngoscopy was done by a well experienced anaesthetist & endotracheal intubation was accomplished within 20 secs with an appropriate sized cuffed endotracheal tube. A longer acting muscle relaxant Inj. Vecuronium 0.1mg/kg was given. In scenario of an unanticipated difficult intubation, the patient had been omitted from the study. BP (SBP, DBP and MAP) and HR were immediately recorded after intubation and subsequently at 1min, 3mins, 5mins & 10mins post intubation.

The observation was tabulated as follow: -

| TIME | BASE LINE | PRIOR TO LARYNGOSCOPY | 1 MIN | 3 MIN | 5 MIN | 10 MIN |
|---|---|---|---|---|---|---|
| Heart Rate | | | | | | |
| Systolic BP | | | | | | |
| Diastolic BP | | | | | | |
| Mean BP | | | | | | |

**Statistical Analysis:**

"The study is focused on comparison of two groups. For the continuous quantitative variables mean and standard deviation will be calculated. The inter group continuous variables will be compared using suitable tools of statistics like unpaired student's t test. Two quantitative variables, within a group, will be compared using student's paired t test.

Discrete variables will be represented by median. Suitable graphs will be used to depict the comparison.

The categorical data will be expressed in terms of rates, ratios and percentages. The association between the outcome, clinical and demographic characteristics will be tested using Chi-square test or Fisher's exact test.

Nonparametric tests will be used for discrete variables.

For all the tests the value of p less than 5% (0.05) will be considered significant."

# RESULTS

This study titled **"TO COMPARE THE EFFECTS OF ORAL MELATONIN VERSUS ORAL PREGABALIN FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ADULT PATIENTS UNDERGOING GENERAL ANESTHESIA. A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL."**was conducted.

60 patients were enrolled in our study. Considering both inclusion & exclusion criteria, these 60 patients were randomized into 2 groups of 30 patients in each.

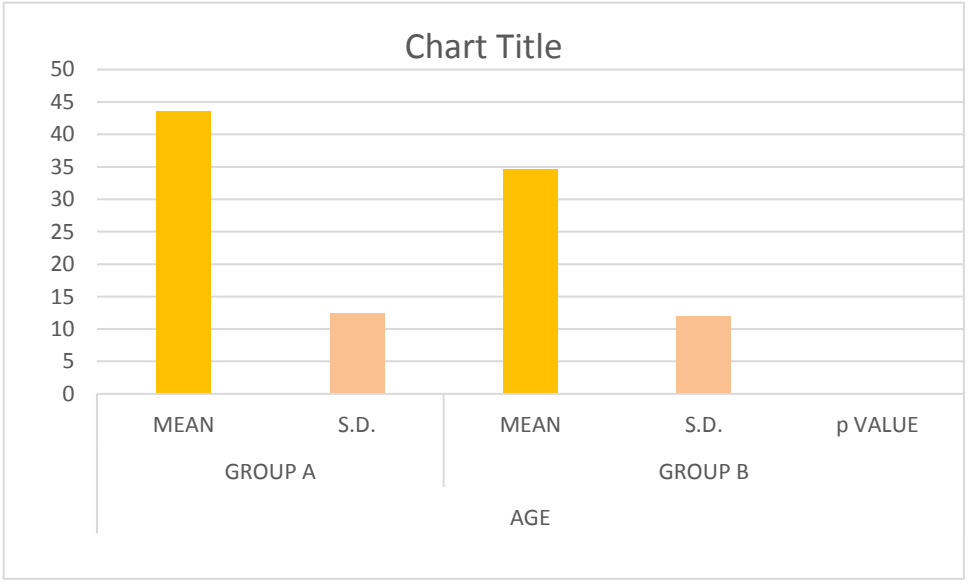
The data was tabulated on Microsoft Excel which was represented as Mean and Standard for all sets of data. Students "t" test has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameter and graphs and tables were generated using Microsoft Excel and Word.

**AGE DISTRIBUTION:**

In group A, the patient's age was distributed from 18 yrs to a maximum of 60 yrs. In Group B, the age group was distributed from 18 yrs to a maximum of 59 yrs. The mean age in Group A was 43.53 yrs and yielded a standard deviation (SD) of 12.43, in Group B the mean age was 34.60 years and yielded a SD of 11.93. The p-value was 0.0062 concluding that the age distribution in the two groups comparable.

| AGE | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| GROUP A | | | | GROUP B | | | | | |
| MEAN | S.D. | MINIMUM | MAXIMUM | MEAN | S.D. | MINIMUM | MAXIMUM | p VALUE | INFERENCE |
| 43.53 | 12.43 | 20 | 60 | 34.60 | 11.93 | 18 | 59 | 0.0062 | VS |

**Table 1: Mean Age**



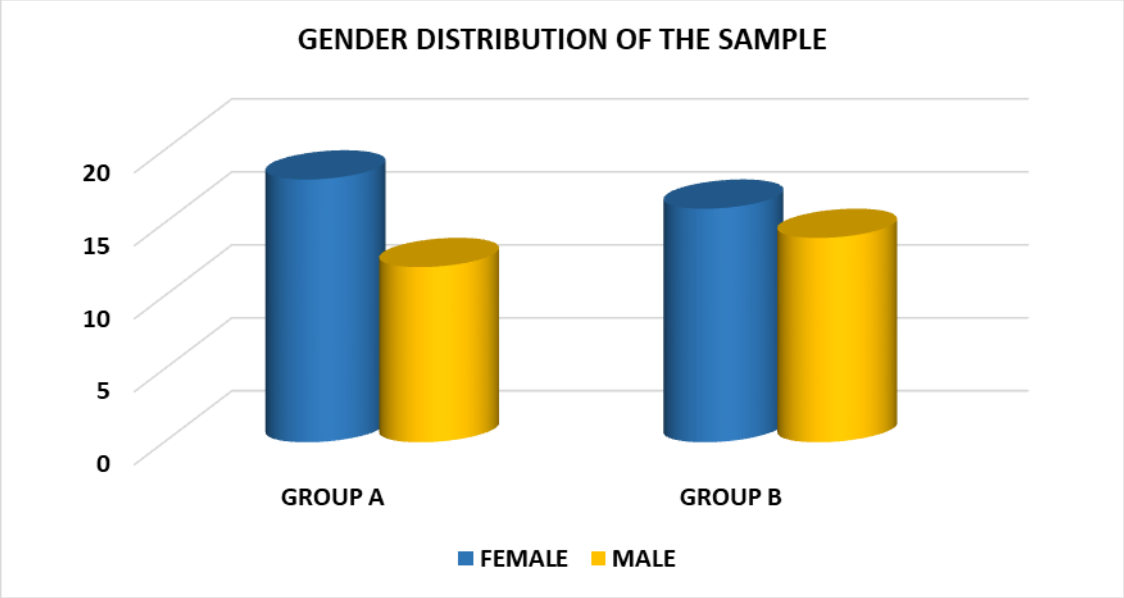

**Graph 1: Mean Age**

**GENDER DISTRIBUTION**:

In Group A there were 18 females and 12 males. In Group B there were 16 females and 14 males. The distribution of gender across both the groups was comparable.

| GENDER | GROUP A | GROUP B |
|---|---|---|
| **FEMALE** | 18 | 16 |
| **MALE** | 12 | 14 |
| **TOTAL** | 30 | 30 |

**Table 2: Gender Distribution**




**Graph 2: Gender Distribution**

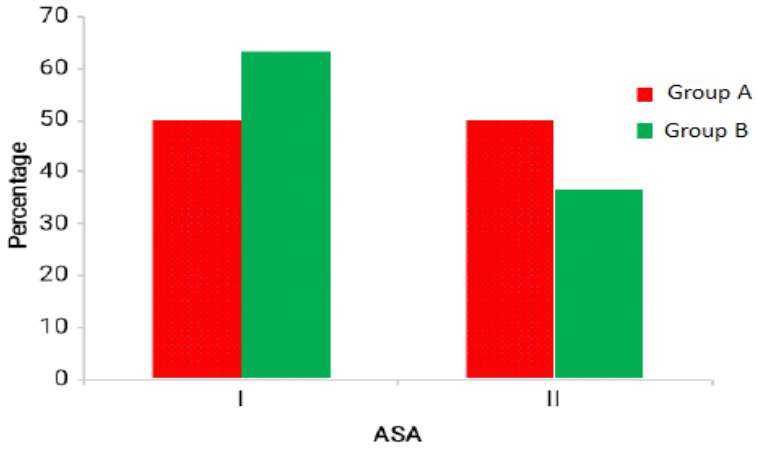
**ASA STATUS**:

There were 15 patients in Group A who were ASA I patients whereas 15 patients were ASA II. Whereas group B had 19 patients who were ASA I while 11 were of ASA II status.

**DISTRIBUTION OF ASA**

| | GROUP A | GROUP B | TOTAL |
|---|---|---|---|
| **ASA I** | 15 | 19 | 34 |
| **ASA II** | 15 | 11 | 26 |
| **TOTAL** | 30 | 30 | 60 |

**Table 3: ASA Status**



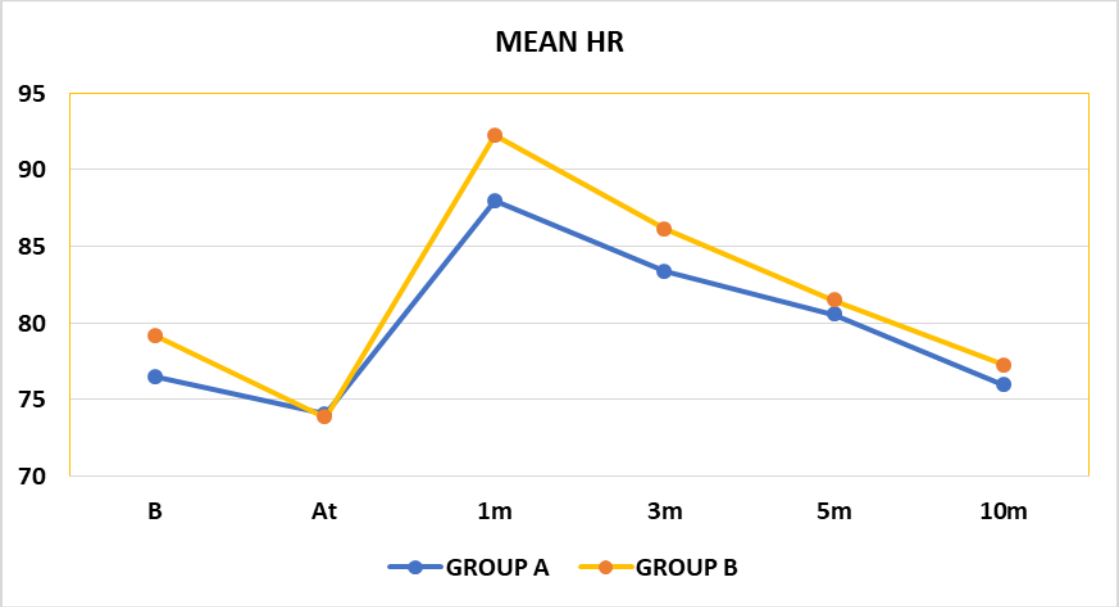

**Graph 3: ASA Status**

Two hours prior to the surgery patients were pre-medicated with oral tablet melatonin or pregabalin based on the computer-generated group. Followed by which endotracheal intubation is done and hemodynamic parameters which are HR, SBP, DBP, MAP are recoded at baseline and intervals of: At induction (AT),1 minute,3 minutes,5 minutes,10 minutes and compared as follow

## HEART RATE:

| | HR | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GROUP A | | | | GROUP B | | | | | |
| | MEAN | S.D. | MINIMUM | MAXIMUM | MEAN | S.D. | MINIMUM | MAXIMUM | p VALUE | INFERENCE |
| **B** | 76.47 | 6.67 | 62 | 89 | 79.17 | 7.54 | 68 | 102 | 0.1474 | NS |
| **At** | 74.03 | 8.29 | 60 | 96 | 73.83 | 6.47 | 63 | 88 | 0.9174 | NS |
| **1m** | 87.97 | 8.41 | 68 | 104 | 92.23 | 9.15 | 72 | 116 | 0.0651 | NS |
| **3m** | 83.37 | 7.63 | 65 | 106 | 86.10 | 9.00 | 74 | 113 | 0.2097 | NS |
| **5m** | 80.53 | 6.27 | 68 | 98 | 81.47 | 8.30 | 70 | 109 | 0.6248 | NS |
| **10m** | 75.93 | 4.57 | 65 | 84 | 77.23 | 8.03 | 68 | 106 | 0.4442 | NS |

**Table 4: Comparison Of Heart Rate Between The Two Groups**



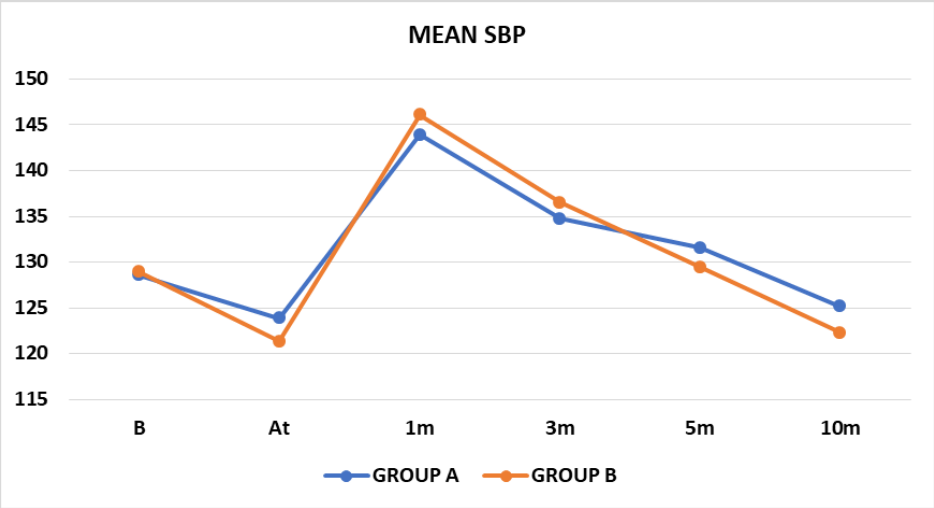

**Graph 4: Mean Heart Rate**

In group A the mean heart rate at baseline is 76.47 and in group B it is 79.17 with p-value of 0.1474 which wasn't much significant. At induction, mean in group A is 74.03 & 73.83 in group B with a p-value of 0.9174 which wasn't significant. Similar observations were seen at 1,3,5,10 minutes. Hence both the drugs reduced the heart rate similarly and were comparable.

## SYSTOLIC BLOOD PRESSURE:

| | SBP | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GROUP A | | | | GROUP B | | | | | |
| | MEAN | S.D. | MINIMUM | MAXIMUM | MEAN | S.D. | MINIMUM | MAXIMUM | p VALUE | INFERENCE |
| B | 128.57 | 10.96 | 100 | 142 | 128.93 | 8.83 | 110 | 148 | 0.8870 | NS |
| At | 123.90 | 9.49 | 106 | 140 | 121.33 | 9.42 | 104 | 143 | 0.2975 | NS |
| 1m | 143.93 | 12.03 | 112 | 161 | 146.10 | 11.46 | 112 | 167 | 0.4780 | NS |
| 3m | 134.73 | 10.95 | 110 | 154 | 136.50 | 8.30 | 116 | 148 | 0.4842 | NS |
| 5m | 131.57 | 8.53 | 109 | 148 | 129.43 | 6.82 | 110 | 138 | 0.2892 | NS |
| 10m | 125.17 | 7.69 | 104 | 137 | 122.30 | 5.59 | 110 | 131 | 0.1041 | NS |

**Table 5: Comparision Of Systolic Blood Pressure Between The Two Groups**



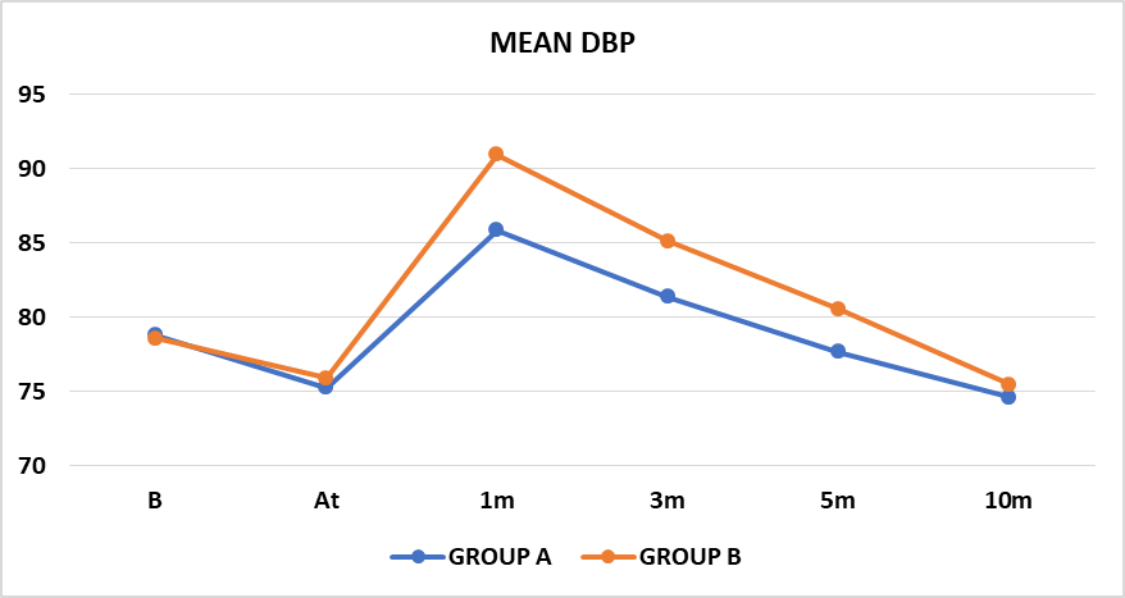

**Graph 5: Mean Systolic Blood Pressure**

In group A, mean SBP was 128.57 & in group B, 128.93 was the mean value with a p-value of 0.8870 which was found to be not significant. At induction the mean SBP was 123.90 in group A & in group B the mean is 121.33 with p-value of 0.2975 which isn't significant. At 1 minute after intubation in group A the mean SBP is 143.93 & in group B it is 146.10 with a p-value of 0.4780 which isn't significant. It was observed that both the drugs have similar effect at 3,5,10 minutes and neither had superior effect when compared.

## DIASTOLIC BLOOD PRESSURE:

| | DBP | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GROUP A | | | | GROUP B | | | | | |
| | MEAN | S.D. | MINIMUM | MAXIMUM | MEAN | S.D. | MINIMUM | MAXIMUM | p VALUE | INFERENCE |
| **B** | 78.77 | 7.46 | 60 | 92 | 78.53 | 7.87 | 62 | 96 | 0.9066 | NS |
| **At** | 75.23 | 6.03 | 64 | 88 | 75.90 | 7.76 | 60 | 97 | 0.7114 | NS |
| **1m** | 85.83 | 9.12 | 65 | 100 | 90.93 | 9.14 | 64 | 105 | 0.0346 | S |
| **3m** | 81.37 | 7.97 | 64 | 91 | 85.10 | 9.29 | 61 | 98 | 0.1001 | NS |
| **5m** | 77.63 | 5.93 | 62 | 85 | 80.53 | 5.54 | 69 | 90 | 0.0553 | NS |
| **10m** | 74.60 | 5.89 | 60 | 85 | 75.43 | 5.28 | 66 | 88 | 0.5662 | NS |

**Table 6: Comparision Of Mean Diastolic Blood Pressure Between The Two Groups**



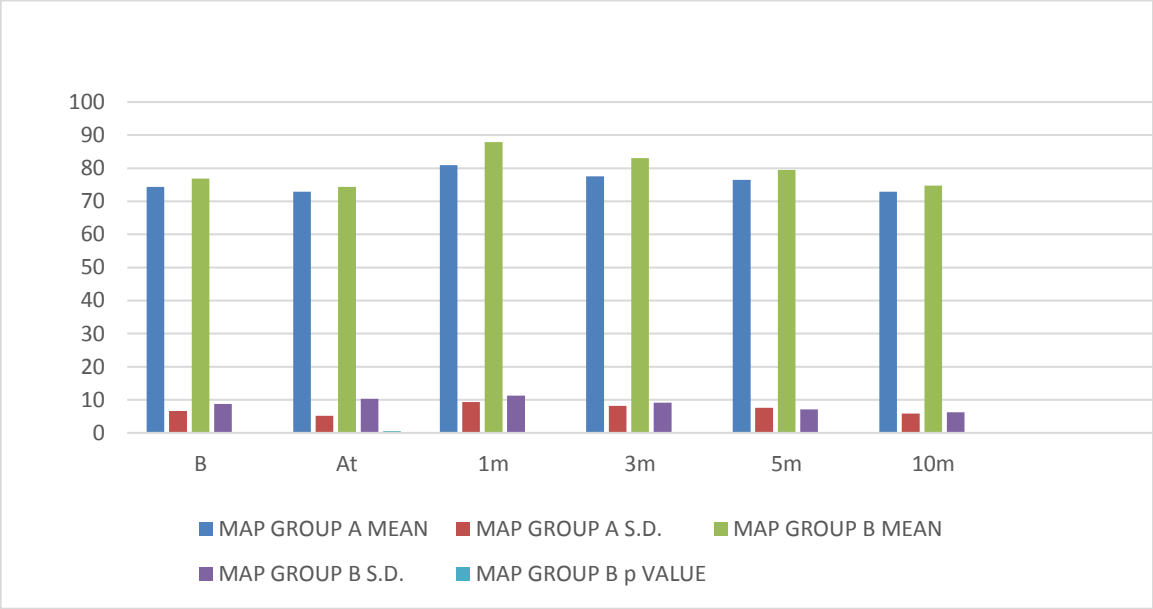

**Graph 6: Mean Diastolic Blood Pressure**

In group A, at baseline mean of DBP is 78.77 & in group B the mean was 78.53 with p-value of 0.9066. At induction the mean DBP in Group A is 75.23 & in Group B was 75.90 with p value of 0.7114. At 1 minute after intubation in group A the mean DBP was 85.83 and in group B it was 90.93 with p value of 0.0346 which was found to be significant when compared. Group A has shown a better control of DBP at 1 minute after intubation. Whereas at 3,5,10 minutes both the drugs had similar effects on DBP.

## MEAN ARTERIAL PRESSURE:

| | MAP | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GROUP A | | | | GROUP B | | | | | |
| | MEAN | S.D. | MINIMUM | MAXIMUM | MEAN | S.D. | MINIMUM | MAXIMUM | p VALUE | INFERENCE |
| B | 74.40 | 6.63 | 60 | 92 | 76.90 | 8.72 | 68 | 100 | 0.2164 | NS |
| At | 72.93 | 5.15 | 65 | 88 | 74.37 | 10.30 | 62 | 112 | 0.4980 | NS |
| 1m | 80.97 | 9.29 | 64 | 102 | 87.90 | 11.23 | 64 | 117 | 0.0116 | S |
| 3m | 77.60 | 8.18 | 65 | 98 | 83.10 | 9.17 | 69 | 110 | 0.0173 | S |
| 5m | 76.47 | 7.61 | 63 | 94 | 79.47 | 7.14 | 68 | 103 | 0.1208 | NS |
| 10m | 72.93 | 5.79 | 60 | 88 | 74.73 | 6.21 | 64 | 90 | 0.2505 | NS |

**Table 7: Comparision Of Mean Arterial Pressure Between Two Groups**




**Graph 7: Comparison Of Mean Arterial Pressure Between Two Groups**

In Group A, the mean MAP is 74.40 and in group B it is 76.90 with a p-value of 0.2164 which isn't significant. At 1 minute the mean of MAP in group A was 80.97 in group B the mean was 87.90 with a p-value of 0.0116 which found to be significant. At 3 min the mean MAP of Group A is 77.60 & in Group B it is 83.10 with a p-value of 0.0173 which is significant. The MAP was attenuated significantly in group A at 1, 3 minutes post-intubation whereas at 5,10 minutes both the drugs showed statistically similar effect.

# DISCUSSION

"General anaesthesia (GA) is a state of controlled loss of consciousness with provided analgesia." To maintain airway endotracheal intubation is done by laryngoscopy. It helps in securing airway and keeping it safe from aspiration and also aid in delivering mixture of anaesthetic gases as desired. Laryngoscopy and endotracheal intubation will result in stressor response and due to this there will be an increase in pulse rate, MAP[36], increased intracranial pressure (ICP) & also increased intraocular pressure (IOP). The undesired effects are due to stimulation of mechanoreceptors which are present in the walls of pharynx, epiglottis & vocal cords.

**Reid & Brace**[36] described the changes in haemodynamics which occur from laryngoscopy. It was observed that after direct laryngoscopy (DL), there was increase in haemodynamics within seconds and a stress response too was followed with endotracheal intubation. This stressor response is seen within 5 secs of laryngoscopy, peaks at 1-2 minutes & returns to the normal range by 5mins. Normal patients will endure the haemodynamic changes well and patients with known cardiovascular and cerebrovascular diseases may have detrimental effect because of the hemodynamic changes which can result in complications like pulmonary oedema, myocardial ischaemia (MI), arrhythmias, cardiac failure & cerebrovascular accidents.

To prevent these complications and attenuate the stressor response numerous drug regimens have been used like lignocaine, opioids, nitroglycerine, calcium channel blockers and beta blockers.

A factor where time taken for laryngoscopy influenced on pressor response study was done by **R.K.Stoeltings et al(1977)[31]**, where they concluded that the near maximal pressor response is seen at 45secs of laryngoscopy with no added increase if

laryngoscopy is sustained. It was determined that to reduce stressor response to laryngoscopy & intubation, the duration of laryngoscopy should be less 30 sec.

The other factors where intubating condition play a role in generating pressor response. To administer anticholinergic like glycopyrrolate which is an anti-sialagogue. it helps to reduce secretions and provide good intubating condition. Therefore, administering glycopyrrolate injection as a premedication will produce ideal intubation condition by reducing secretions.

**Gupta P[6]**, where 60 patients with ASA status Grade I and II posted for non-emergency surgeries under general anaesthesia(GA) have been selected & divided into 2 equal groups; Group C (control) & Group M (melatonin) where they were orally given placebo & tablet melatonin 6 mg, 120 mins prior surgery. The systolic (SBP), diastolic (DBP), mean arterial pressures (MAP) and Heart rate (HR) were recorded prior to surgery, laryngoscopy and intubation, and also at 1, 3, 5, and 10 minutes(min). A significant rise in HR & blood pressure (BP) at the time of laryngoscopy was observed which continued till 10mins post intubation. In the melatonin group it had been observed that there was an irrelevant rise in HR at laryngoscopy & intubation, which also reduced within 1 min after intubation.

**Puja Thapa[11]** conducted a doubled blinded randomised study. In this study 50 patients with treated hypertension were enrolled and divided into 2 equal groups

One group received 75mg of pregabalin capsule and other group received multivitamin capsule 60 minutes prior to induction of general anaesthesia. It was concluded that oral dose of 75mg of pregabalin was efficient and significantly reduced haemodynamic response to laryngoscopy and intubation. It aided in attenuating the haemodynamic response to laryngoscopy & intubation with acceptable sedation levels.

**Dheer Singh**[15] conducted a randomized double blinded study done on 60 patients of ASA physical grade I&II, who were undergoing planned non-emergency laparoscopic cholecystectomy were randomized into 2 groups. They received either placebo or 150mg pregabalin orally, 60mins prior to anaesthesia induction. Anxiety was recorded with the help of Visual analog scale (VAS) before & 60mins after drug administration. Hemodynamic parameters such as the HR, SBP, DBP, MAP was noted before, 60mins after drug administration, intraoperatively 2, 4, 6, 8 & 10mins post intubation. It was concluded that pregabalin is an effective drug in decreasing the preoperative anxiety & the stressor response to endotracheal intubation.

The study we conducted intended to know the effectiveness to attenuate the haemodynamic response where we compared oral administration of melatonin in a dose of 6mg with pregabalin of 150mg and haemodynamic parameters which included SBP, DBP, MAP & HR were noted.

Our study was conducted after the approval of ethical committee, obtaining consent from patients. 60 patients who were listed to undergo elective surgical procedures under GA were randomly allocated into 2 groups; Group A and Group B.

Group A patients received 2 tablets 3mg each a total of 6mg melatonin orally 120minutes prior to intubation whereas Group B also received two tablets of oral pregabalin 75mg each a total of 150mg was given.

To distinguish the efficacy of administering oral melatonin with oral pregabalin and their role in decreasing the haemodynamic stressor response to laryngoscopy & endotracheal intubation. HR, SBP, DBP and MAP were compared in both the groups.

The demographic profile of Age, ASA physical status and Gender showed no significant difference statistically. Therefore, there was no difference with the Age, Gender and ASA status of patient.

**HEART RATE**

In group A, an increase in HR at 1min was observed on comparison to baseline which was significant & later reached the baseline value at 3mins followed with further significant decrease in the value which was observed at duration of 5minutes and 10minutes.

In group B, an increase in HR which was similar to group A followed by decrease in the value seen at 1min which was significant.

Therefore, we infer that decrease in Heart rate was observed in both the Groups and Group B had a statistically significant decrease in heart rate compared to the other group.

**SYSTOLIC BLOOD PRESSURE**

In Group A, an increase in SBP at 1min which was not significant statistically. It was followed by a steady decline observed at 3mins, 5mins & 10mins which had significant statistical difference when they are compared to baseline readings.

Similarly, in Group B, an increase in SBP at 1min was followed with a gradual decline at 3mins, 5mins & 10mins which was also seen in Group A.

Hence, it was concluded that there was a similar decrease in SBP in both the groups.

**DIASTOLIC BLOOD PRESSURE**

In Group A, an increase in DBP at 1min was noted which was not significant statistically. It was followed with a gradual decrease in DBP which was seen at 3mins, 5mins & 10mins. These observations showed significant statistical difference when compared to the baseline readings.

Similarly, in Group B, an increase in DBP at 1minwas noted followed by a gradual decrease at 3mins, 5mins & 10mins.

However, when DBP was compared at 1min between both the groups Group A had significant control of DBP.

**MEAN ARTERIAL PRESSURE**

In Group A, an increase in MAP at 1min was observed which was not significant statistically. It was followed by a steady decline which was seen at 3mins, 5mins & 10mins. These values showed difference significantly when they were compared to baseline readings.

In Group B, an increase in MAP at 1min followed by steady decline at 3mins, 5mins & 10mins which was also see in Group A.

However, both the drugs showed significant hemodynamic attenuation but at 1min,3min post-intubation Group A has shown statistically significant attenuation when compared to Group B

As seen in above observations oral administration melatonin and pregabalin did produce hemodynamic stability which was similar in both the groups. However, group which received melatonin had better control on DBP and MAP. Patients from neither groups experienced any adverse events after the oral intake of their respective drug.

# CONCLUSION

Oral administration of melatonin 6mg or pregabalin 150 mg at 120 minutes prior to laryngoscopy and intubation did provide significant haemodynamic stability which were similar in both the groups and there were no adverse effects seen with both the drugs. However, patients who received melatonin had statistically better control of Diastolic Blood Pressure and Mean Arterial Pressure at 1min and 3min post-intubation when compared to pregabalin group.

# SUMMARY

The present study entitled **"TO COMPARE THE EFFECTS OF ORAL MELATONIN VERSUS ORAL PREGABALIN FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ADULT PATIENTS UNDERGOING GENERAL ANESTHESIA. A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL."** was conducted at "KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehru Nagar, Belagavi- 590010".

After obtaining clearance from hospital's ethical committee, 60 patients of ASA I and II between age group 18-60 years were randomized into 2 groups with 30 patients in each.

Group A- Participants were given (n=30) two tablets of melatonin 3mg each total(6mg) orally 120minutes prior to surgery.

Group B- Patients (n=30) received two tablets of pregabalin 75mg each total of 150mg 120minutes prior to surgery.

General anaesthesia was induced as per standard technique. HR, SBP, DBP, MAP and SpO2 were recorded in both the groups. The demographics were identical in both the groups.

We observed that HR and SBP were similar in both the groups and in Group A patients had better hemodynamic control of DBP at 1Minute and MAP at 1minute and 3minute. The pressor response returned to baseline after 5 minutes in both the groups.

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## Annexure -I

## Ethical Clerance

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 180. Date: 24/12/2019

To.

BA0119009

PG student in Anaesthesiology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"TO COMPARE THE EFFECTS OF ORAL MELATONIN VERSUS ORAL PREGABALIN FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ADULT PATIENTS UNDERGOING GENERAL ANESTHESIA. A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

**(Dr. Anita Dalal)**
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

**(Dr. Roopa M Bellad)**
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

## ANNEXURE -II

## INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

"TO COMPARE THE EFFECTS OF ORAL MELATONIN VERSUS ORAL PREGABALIN FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ADULT PATIENTS UNDERGOING GENERAL ANESTHESIA. A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL."

PRINCIPAL INVESTIGATOR:

CO-INVESTIGATOR :

**INTRODUCTION AND PURPOSE:**

The present study is conducted among patients who are undergoing various elective surgeries under general anaesthesia with endotracheal intubation in the department of Anaesthesiology at KLE's Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belagavi. You are requested to participate in the study and your participation is completely voluntary.

The aim of the study is to compare the effectiveness of oral melatonin versus oral pregabalin for the attenuation of hemodynamic response to laryngoscopy and endotracheal intubation in patients undergoing general anaesthesia.

**PROCEDURE:**

If you agree to participate in this study, the relevant data will be collected as per the proforma. After getting inducted in the study, you will be undergoing the surgery under general anaesthesia and will be randomly allocated to either of the study groups and administered the respective drug 120minutes before the surgery, after which BP (SBP, DBP and MAP) and heart rate will be recorded at baseline, at induction and after intubation at 1 min, 3 min, 5 min and 10 min.

**BENEFITS:**

Patient will not be eligible for any kind of monetary benefits or free services by virtue of your participation in the study.

**RISKS:**

Methods and drugs applied to do the study are safe.

**COST OF PARTICIPATION:**

The cost of the Investigation and other indirect expenses will be borne by the Investigator.

**PRIVACY AND CONFIDENTIALITY:**

The results of the study may be published in journals for scientific purposes. However, your identity will not be revealed. All information collected will be coded so that no one other than the investigator will know your identity.

**WITHDRAWAL FROM THE STUDY:**

You can withdraw from the study at any time if you wish to do so.

**ALTERNATIVES:**

In case you opt out of the study, it will not affect your relationship with KLES Dr. Prabhakar Kore Hospital.

**AUTHORIZATION TO PUBLISH THE RESULTS:**

The researcher may use the information gathered from this study for presentation in scientific meetings. However, your identity will not be revealed.

**INSTITUTIONAL /SPONSORS POLICY:**

In the event of any drug reaction or injury during the procedure, related to this study, no reimbursement or compensation will be given by law. However, treatment will be made available at KLES Hospital & MRC, Belgaum. If you face any untoward event, you may contact–Department of Anaesthesiology, KLE's Hospital & MRC.

**LEGAL RIGHTS**: By signing this consent form, you are not waiving any of your legal rights.

**CONSENT SUMMARY:**

I have been explained all the contents of this consent form in my local language and having understood and clarified all my queries about the study to the best of my knowledge, I hereby give my voluntary consent for participation in the study. I do sign the informed consent form in front of an eyewitness whom I recognize.

Subject Name: _____

Guardian Name: _____ Signature/Left thumb Print: _____

Investigators Name: _____ Signature: _____

Witness Name: _____ Signature: _____

Date: _____

Place: _____

**CONSENT STATEMENT TO PARTICIPATE IN A RESEARCHSTUDY**

I, Mr./Mrs./Miss._____ voluntarily agree to take part in this study, by signing this consent form I am not giving up my legal rights. I may withdraw from the study at any time. I am signing the consent form after having read, or been read to me in the vernacular language including risks and the benefits and having all queries cleared.

Signature of the study patient_____

Name of Study patient_____

Name and Signature of Witness_____

_____

Name and signature of investigator_____

_____

DATE: _____ PLACE: _____

**Annexure -III**

**PROFORMA**

**TITLE:- "TO COMPARE THE EFFECTS OF ORAL MELATONIN VERSUS ORAL PREGABALIN FOR ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ADULT PATIENTS UNDERGOING GENERAL ANESTHESIA. A ONE YEAR HOSPITAL BASEDRANDOMIZED CLINICAL TRIAL."**

Patients Name : I.P No. :

Age : Gender :

Date of operation : Diagnosis : -

Proposed surgery: Anaesthesiologist :

Chief Complaints:

**Past History:**

- H/O Previous Anaesthetic procedure/Previous surgeries
- H/O Allergy to melatonin, pregabalin or any other drug

***General physical examination:***

PR : BP : RR

**Systemic examination:**

RS : CNS :

CVS : GIT :

**Airway Assessment** – **Spine-**

**Investigations**

Hb% : Urine routine :

Blood urea : Serum creatinine:

FBS : CXR : ECG:

**Preoperative physical status**

ASA Grade I II III IV V

Group Allotted:

The observation will be tabulated as follow:

| TIME | BASELINE | AT INDUCTION | 1 MIN | 3 MIN | 5 MIN | 10 MIN |
|---|---|---|---|---|---|---|
| Heart Rate | | | | | | |
| Systolic BP | | | | | | |
| Diastolic BP | | | | | | |
| Mean BP | | | | | | |

- SIGNATURE OF THE ANAESTHESIOLOGIST - _____
- SIGNATURE OF THE WITNESS - _____

- SIGNATURE OF THE PRINCIPAL INVESTIGATOR - _____

# ANNEXURE IV – PHOTOGRAPHS

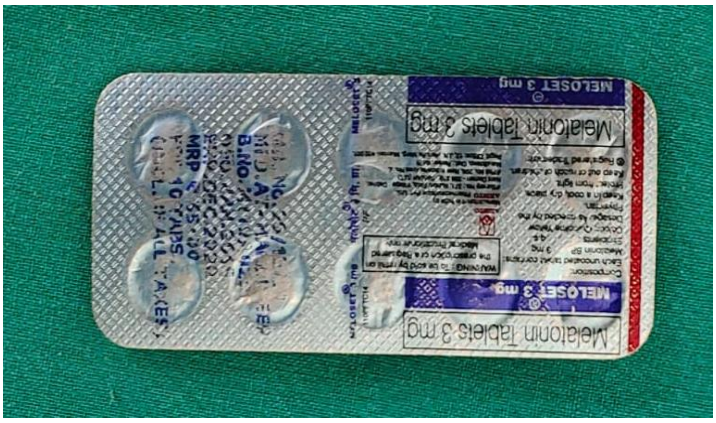


**Photo 1: Melatonin Tablet**


**Photo 2: Pregabalin**

## ANNEXURE – V

## KEYS TO MASTERCHART

| | | |
|---|---|---|
| IP NO | - | IN PATIENT NUMBER |
| M | - | MALE |
| F | - | FEMALE |
| HR | - | HEART RATE |
| SBP | - | SYSTOLIC BLOOD PRESSURE |
| DBP | - | DIASTOLIC BLOOD PRESSURE |
| MAP | - | MEAN ARTERIAL BLOOD PRESSURE |
| m | - | MINUTES |

# ANNEXURE – VI

## MASTER CHART

## GROUP A - MELATONIN

| S.No | IP No | Age /sex | HR | | | | | | SBP | | | | | | DBP | | | | | | MAP | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | B | At | 1m | 3m | 5m | 10m | B | At | 1m | 3m | 5m | 10m | B | At | 1m | 3m | 5m | 10m | B | At | 1m | 3m | 5m | 10m |
| 1 | 1025040 | 33/M | 84 | 92 | 86 | 84 | 80 | 76 | 124 | 106 | 138 | 112 | 109 | 104 | 78 | 70 | 79 | 82 | 82 | 76 | 92 | 82 | 88 | 90 | 94 | 88 |
| 2 | 14148 | 48/F | 84 | 82 | 84 | 80 | 76 | 74 | 142 | 130 | 128 | 127 | 125 | 123 | 84 | 78 | 74 | 70 | 70 | 71 | 78 | 88 | 84 | 80 | 75 | 70 |
| 3 | 1025270 | 20/F | 80 | 96 | 94 | 90 | 88 | 84 | 100 | 128 | 114 | 110 | 110 | 108 | 60 | 74 | 70 | 72 | 70 | 66 | 60 | 70 | 74 | 66 | 63 | 60 |
| 4 | 1000130 | 45/F | 64 | 60 | 68 | 65 | 69 | 65 | 130 | 140 | 142 | 138 | 134 | 130 | 70 | 78 | 78 | 74 | 80 | 82 | 68 | 72 | 74 | 70 | 68 | 67 |
| 5 | 14532 | 60/M | 62 | 60 | 82 | 81 | 78 | 76 | 132 | 128 | 145 | 140 | 136 | 132 | 92 | 88 | 96 | 88 | 80 | 76 | 82 | 80 | 72 | 70 | 68 | 71 |
| 6 | 3014433 | 47/M | 82 | 80 | 89 | 82 | 80 | 76 | 138 | 134 | 142 | 136 | 134 | 127 | 78 | 74 | 84 | 78 | 72 | 81 | 80 | 76 | 90 | 82 | 78 | 75 |
| 7 | 1007516 | 55/F | 72 | 70 | 89 | 81 | 78 | 71 | 121 | 116 | 154 | 138 | 131 | 127 | 81 | 75 | 90 | 88 | 84 | 79 | 74 | 68 | 89 | 79 | 81 | 71 |
| 8 | 992214 | 50/F | 70 | 74 | 92 | 78 | 74 | 68 | 112 | 106 | 138 | 131 | 128 | 111 | 78 | 64 | 94 | 82 | 76 | 71 | 69 | 66 | 86 | 80 | 74 | 68 |
| 9 | 14530 | 46/M | 89 | 80 | 92 | 81 | 79 | 76 | 142 | 131 | 150 | 141 | 138 | 130 | 88 | 80 | 100 | 87 | 80 | 76 | 72 | 68 | 82 | 79 | 78 | 76 |
| 10 | 14452 | 53/F | 77 | 74 | 88 | 84 | 82 | 77 | 113 | 111 | 139 | 132 | 129 | 123 | 71 | 68 | 84 | 79 | 78 | 71 | 69 | 70 | 75 | 73 | 70 | 72 |
| 11 | 14459 | 47/F | 81 | 70 | 89 | 84 | 79 | 78 | 136 | 122 | 140 | 132 | 128 | 124 | 76 | 72 | 78 | 73 | 70 | 69 | 69 | 68 | 72 | 70 | 69 | 65 |
| 12 | 996994 | 28/F | 80 | 74 | 76 | 78 | 74 | 75 | 100 | 107 | 142 | 118 | 127 | 122 | 60 | 70 | 80 | 70 | 80 | 77 | 64 | 68 | 64 | 65 | 70 | 65 |
| 13 | 986122 | 21/F | 72 | 70 | 68 | 72 | 78 | 82 | 128 | 117 | 125 | 117 | 124 | 129 | 74 | 68 | 65 | 64 | 68 | 76 | 68 | 70 | 65 | 67 | 68 | 70 |
| 14 | 14495 | 35/F | 72 | 78 | 104 | 106 | 98 | 80 | 138 | 135 | 150 | 133 | 130 | 127 | 82 | 86 | 98 | 87 | 80 | 78 | 72 | 68 | 102 | 98 | 94 | 79 |
| 15 | 3014358 | 58/M | 68 | 72 | 84 | 86 | 78 | 74 | 136 | 140 | 148 | 144 | 138 | 132 | 74 | 70 | 76 | 73 | 72 | 70 | 69 | 70 | 71 | 69 | 70 | 70 |
| 16 | 999374 | 22/M | 80 | 76 | 72 | 74 | 78 | 72 | 130 | 110 | 112 | 123 | 128 | 124 | 80 | 70 | 68 | 64 | 62 | 60 | 78 | 74 | 68 | 66 | 65 | 69 |
| 17 | 14123 | 45/F | 64 | 60 | 79 | 70 | 68 | 66 | 117 | 126 | 1566 | 131 | 128 | 126 | 88 | 84 | 81 | 79 | 74 | 71 | 70 | 73 | 72 | 70 | 73 | 68 |
| 18 | 14479 | 35/F | 84 | 78 | 94 | 80 | 76 | 72 | 139 | 131 | 139 | 126 | 122 | 112 | 80 | 76 | 85 | 81 | 68 | 62 | 71 | 75 | 70 | 72 | 77 | 68 |
| 19 | 1032394 | 52/F | 78 | 72 | 91 | 88 | 82 | 78 | 128 | 121 | 144 | 141 | 138 | 131 | 69 | 67 | 90 | 88 | 82 | 79 | 74 | 70 | 89 | 85 | 80 | 78 |
| 20 | 1026946 | 48/F | 68 | 60 | 88 | 80 | 78 | 81 | 134 | 121 | 149 | 138 | 136 | 137 | 84 | 76 | 89 | 85 | 81 | 85 | 69 | 65 | 75 | 70 | 72 | 71 |
| 21 | 1027979 | 51/F | 82 | 81 | 94 | 90 | 94 | 81 | 141 | 138 | 155 | 147 | 148 | 134 | 88 | 84 | 91 | 89 | 84 | 82 | 85 | 80 | 89 | 88 | 86 | 81 |
| 22 | 1027701 | 30/F | 78 | 81 | 89 | 85 | 82 | 74 | 131 | 125 | 141 | 138 | 132 | 128 | 78 | 74 | 89 | 85 | 80 | 72 | 74 | 72 | 85 | 82 | 80 | 75 |
| 23 | 1028228 | 38/M | 77 | 76 | 90 | 88 | 82 | 74 | 131 | 124 | 140 | 136 | 131 | 122 | 82 | 79 | 92 | 88 | 81 | 70 | 79 | 75 | 84 | 82 | 78 | 71 |
| 24 | 1028613 | 22/F | 74 | 68 | 90 | 82 | 78 | 74 | 132 | 122 | 148 | 131 | 128 | 120 | 78 | 72 | 90 | 88 | 81 | 72 | 74 | 71 | 80 | 78 | 78 | 75 |
| 25 | 1029072 | 46/M | 78 | 70 | 94 | 85 | 82 | 78 | 131 | 124 | 158 | 149 | 135 | 124 | 85 | 81 | 94 | 90 | 85 | 79 | 80 | 78 | 89 | 81 | 80 | 76 |
| 26 | 1029282 | 57/M | 74 | 71 | 91 | 88 | 82 | 78 | 128 | 124 | 161 | 154 | 141 | 131 | 84 | 81 | 94 | 89 | 80 | 79 | 79 | 74 | 89 | 84 | 78 | 78 |
| 27 | 1029145 | 57/F | 81 | 76 | 98 | 89 | 84 | 78 | 138 | 128 | 154 | 141 | 138 | 131 | 84 | 79 | 88 | 82 | 81 | 78 | 81 | 78 | 84 | 81 | 79 | 79 |
| 28 | 1028350 | 60/M | 82 | 74 | 96 | 90 | 88 | 80 | 123 | 118 | 152 | 148 | 138 | 131 | 77 | 70 | 94 | 91 | 84 | 80 | 75 | 71 | 89 | 85 | 82 | 79 |
| 29 | 1028284 | 57/M | 78 | 74 | 94 | 89 | 85 | 78 | 131 | 126 | 156 | 149 | 145 | 127 | 78 | 71 | 92 | 89 | 82 | 78 | 79 | 74 | 89 | 84 | 79 | 75 |
| 30 | 1029594 | 40/M | 79 | 72 | 94 | 91 | 86 | 82 | 131 | 128 | 158 | 141 | 138 | 128 | 82 | 78 | 92 | 86 | 82 | 72 | 78 | 74 | 89 | 82 | 87 | 78 |

# GROUP B - PREGABALIN

| S.No | IP No | Age /sex | HR | | | | | | SBP | | | | | | DBP | | | | | | MAP | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | B | At | 1m | 3m | 5m | 10m | B | At | 1m | 3m | 5m | 10m | B | At | 1m | 3m | 5m | 10m | B | At | 1m | 3m | 5m | 10m |
| 1 | 1040060 | 18/F | 88 | 80 | 93 | 89 | 83 | 80 | 134 | 128 | 157 | 146 | 137 | 126 | 78 | 71 | 102 | 93 | 88 | 81 | 85 | 79 | 98 | 89 | 85 | 85 |
| 2 | 1030419 | 48/F | 79 | 72 | 86 | 81 | 76 | 68 | 148 | 132 | 150 | 142 | 134 | 130 | 91 | 87 | 100 | 96 | 87 | 80 | 100 | 98 | 110 | 102 | 84 | 78 |
| 3 | 1030955 | 37/F | 82 | 76 | 90 | 85 | 80 | 76 | 120 | 112 | 130 | 125 | 120 | 110 | 76 | 70 | 89 | 80 | 75 | 70 | 69 | 66 | 80 | 72 | 69 | 66 |
| 4 | 1029511 | 55/M | 102 | 86 | 116 | 110 | 101 | 94 | 142 | 126 | 150 | 142 | 134 | 131 | 96 | 90 | 102 | 98 | 89 | 88 | 85 | 77 | 95 | 90 | 85 | 80 |
| 5 | 1030583 | 45/M | 76 | 70 | 97 | 90 | 88 | 84 | 137 | 133 | 156 | 148 | 134 | 128 | 82 | 79 | 95 | 90 | 83 | 77 | 78 | 74 | 88 | 85 | 79 | 72 |
| 6 | 1016063 | 39/F | 72 | 66 | 91 | 82 | 78 | 74 | 127 | 124 | 148 | 137 | 130 | 121 | 72 | 70 | 100 | 98 | 90 | 72 | 71 | 70 | 90 | 88 | 84 | 70 |
| 7 | 993150 | 24/F | 74 | 70 | 88 | 84 | 71 | 68 | 129 | 124 | 148 | 138 | 134 | 127 | 84 | 78 | 98 | 88 | 80 | 81 | 74 | 81 | 88 | 84 | 81 | 74 |
| 8 | 1015676 | 57/F | 82 | 80 | 94 | 78 | 76 | 72 | 120 | 110 | 146 | 122 | 118 | 121 | 70 | 68 | 84 | 72 | 70 | 68 | 68 | 62 | 86 | 74 | 68 | 64 |
| 9 | 999374 | 22/M | 84 | 78 | 74 | 76 | 70 | 78 | 110 | 120 | 118 | 116 | 110 | 116 | 70 | 68 | 64 | 62 | 72 | 66 | 68 | 70 | 64 | 69 | 74 | 72 |
| 10 | 1001526 | 23/M | 84 | 70 | 78 | 76 | 75 | 70 | 130 | 119 | 132 | 128 | 125 | 122 | 70 | 72 | 87 | 82 | 80 | 77 | 68 | 62 | 68 | 70 | 68 | 65 |
| 11 | 1031239 | 19/F | 76 | 70 | 88 | 80 | 78 | 74 | 121 | 112 | 141 | 132 | 128 | 122 | 74 | 68 | 82 | 80 | 78 | 76 | 70 | 71 | 75 | 79 | 77 | 76 |
| 12 | 1027371 | 29/M | 74 | 68 | 90 | 86 | 82 | 78 | 131 | 126 | 150 | 144 | 138 | 126 | 79 | 71 | 86 | 80 | 78 | 72 | 76 | 70 | 89 | 84 | 82 | 76 |
| 13 | 1027201 | 43/F | 72 | 66 | 91 | 85 | 80 | 78 | 121 | 117 | 148 | 138 | 131 | 124 | 84 | 72 | 91 | 81 | 78 | 72 | 74 | 68 | 82 | 80 | 78 | 76 |
| 14 | 1025040 | 33/M | 82 | 88 | 112 | 113 | 109 | 106 | 140 | 143 | 167 | 137 | 132 | 121 | 90 | 97 | 100 | 96 | 89 | 78 | 90 | 112 | 117 | 110 | 103 | 90 |
| 15 | 102330 | 30/F | 76 | 78 | 91 | 84 | 80 | 74 | 129 | 124 | 142 | 131 | 127 | 118 | 79 | 81 | 91 | 89 | 82 | 78 | 70 | 68 | 71 | 69 | 74 | 68 |
| 16 | 992938 | 26/F | 79 | 71 | 89 | 81 | 76 | 70 | 128 | 124 | 144 | 138 | 127 | 122 | 77 | 78 | 92 | 89 | 85 | 82 | 68 | 69 | 82 | 80 | 78 | 74 |
| 17 | 1024557 | 31/F | 82 | 76 | 72 | 74 | 78 | 72 | 130 | 110 | 112 | 124 | 126 | 124 | 78 | 70 | 68 | 61 | 69 | 66 | 95 | 83 | 82 | 86 | 84 | 85 |
| 18 | 1051456 | 45/M | 85 | 78 | 89 | 82 | 78 | 70 | 132 | 126 | 158 | 141 | 136 | 126 | 78 | 75 | 82 | 84 | 78 | 72 | 78 | 74 | 86 | 81 | 82 | 78 |
| 19 | 1001354 | 59/M | 82 | 76 | 92 | 82 | 78 | 74 | 134 | 128 | 152 | 146 | 136 | 128 | 79 | 74 | 90 | 88 | 80 | 78 | 78 | 75 | 88 | 86 | 80 | 75 |
| 20 | 1028156 | 28/M | 76 | 70 | 95 | 91 | 86 | 80 | 136 | 125 | 149 | 136 | 128 | 123 | 79 | 72 | 89 | 81 | 78 | 74 | 75 | 70 | 88 | 80 | 78 | 72 |
| 21 | 1019348 | 32/F | 74 | 70 | 88 | 81 | 74 | 70 | 117 | 121 | 144 | 128 | 124 | 112 | 62 | 78 | 91 | 78 | 81 | 74 | 70 | 74 | 80 | 74 | 71 | 70 |
| 22 | 1029745 | 50/M | 72 | 65 | 89 | 81 | 74 | 70 | 126 | 106 | 132 | 126 | 118 | 112 | 66 | 60 | 84 | 76 | 74 | 68 | 71 | 68 | 79 | 72 | 68 | 66 |
| 23 | 1027114 | 50/M | 77 | 74 | 97 | 87 | 80 | 78 | 138 | 134 | 152 | 140 | 138 | 130 | 89 | 85 | 90 | 87 | 80 | 75 | 85 | 87 | 95 | 89 | 85 | 80 |
| 24 | 1040392 | 24/F | 74 | 70 | 94 | 88 | 82 | 78 | 134 | 128 | 151 | 146 | 138 | 127 | 81 | 80 | 90 | 88 | 85 | 82 | 82 | 78 | 89 | 87 | 85 | 82 |
| 25 | 1033696 | 41/F | 99 | 88 | 106 | 100 | 94 | 88 | 138 | 110 | 150 | 142 | 132 | 120 | 89 | 80 | 96 | 90 | 84 | 80 | 85 | 70 | 92 | 89 | 80 | 74 |
| 26 | 1035768 | 24/F | 72 | 78 | 95 | 81 | 78 | 74 | 129 | 126 | 151 | 146 | 136 | 124 | 82 | 84 | 105 | 95 | 77 | 72 | 78 | 72 | 95 | 92 | 85 | 78 |
| 27 | 1035971 | 25/M | 81 | 76 | 91 | 88 | 83 | 80 | 134 | 128 | 153 | 146 | 132 | 126 | 85 | 80 | 95 | 90 | 88 | 81 | 87 | 78 | 90 | 88 | 85 | 80 |
| 28 | 1017454 | 28/M | 72 | 68 | 91 | 82 | 84 | 78 | 121 | 112 | 148 | 138 | 129 | 121 | 71 | 67 | 98 | 94 | 81 | 78 | 68 | 65 | 90 | 80 | 78 | 71 |
| 29 | 1035672 | 27/M | 79 | 74 | 102 | 98 | 89 | 83 | 118 | 108 | 156 | 137 | 126 | 113 | 72 | 74 | 92 | 86 | 79 | 73 | 69 | 71 | 102 | 82 | 78 | 73 |
| 30 | 1024521 | 26/F | 68 | 63 | 98 | 88 | 83 | 78 | 114 | 104 | 148 | 135 | 125 | 118 | 73 | 78 | 95 | 81 | 78 | 72 | 72 | 69 | 98 | 82 | 76 | 72 |