"COMPARATIVE ASSESSMENT OF ORAL CLONIDINE AND ORAL MELATONIN FOR THE MITIGATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND TRACHEAL INTUBATION- A PROSPECTIVE RANDOMISED DOUBLE-BLIND STUDY"

By

Dr. SUNDEEP KALIMISETTY

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, KOLAR, KARNATAKA

In partial fulfilment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

Under the Guidance of

Dr. KIRAN N

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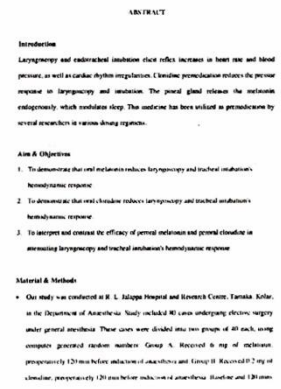


ABSTRACT

Introduction

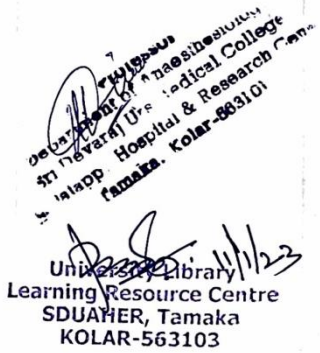
Laryngoscopy and endotracheal intubation elicit reflex increases in heart rate and blood pressure, as well as cardiac rhythm irregularities. Clonidine premedication reduces the pressor response to laryngoscopy and intubation. The pineal gland releases the melatonin endogenously, which modulates sleep. This medicine has been utilized as premedication by several researchers in various dosing regimens.

Aim & Objectives

1. To demonstrate that oral melatonin reduces laryngoscopy and tracheal intubation's hemodynamic response
2. To demonstrate that oral clonidine reduces laryngoscopy and tracheal intubation's hemodynamic response
3. To interpret and contrast the efficacy of perioral melatonin and perioral clonidine in attenuating laryngoscopy and tracheal intubation's hemodynamic response

Material & Methods

- Our study was conducted in B. L. Jalappa Hospital and Research Centre, Tamaka Kolar, in the Department of Anaesthesia. Study included 80 cases undergoing elective surgery under general anesthesia. These cases were divided into two groups of 40 each, using computer generated random numbers. Group A: Received 6 mg of melatonin, preoperatively 120 min before induction of anaesthesia and Group B: Received 0.2 mg of clonidine, preoperatively 120 min before induction of anaesthesia. Baseline and 120 min



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Date: **Dr. SUNDEEP KALIMISETTY**

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ABBREVIATIONS

ASA	AMERICAN SOCIETY OF ANESTHESIOLOGIST
BMR	CENTRAL NERVOUS SYSTEM
C-AMP	CYCLIC ADENOSINE MONOPHOSPHATE
CBF	CEREBRAL BLOOD FLOW
CNS	CENTRAL NERVOUS SYSTEM
CYT-P450	CYTOCHROME P-450
DBP	DIASTOLIC BLOOD PRESSURE
DEPT	DEPARTMENT
DM	DIABETES MELLITUS
DSS	DIGIT SYMBOL SUBSTITUTION
ECT	ELECTROCONVULSIVE THERAPY
EEG	ELECTROENCEPHALOGRAM
EKG	ELECTROKARDIOGRAM
G	GAUGE
GA	GENERAL ANESTHESIA
GABA	GAMMA-AMINOBUTYRIC ACID
GLOSSARY	ABBREVIATIONS
GM	GRAM
GM	GRAM
GNRP	GUANINE NUCLEOTIDE RELEASING PROTEIN
HR	HEART RATE
HTN	HYPERTENSION
I.V	INTRAVENOUS
ICP	MILLIGRAM
IO	INTRAOPERATIVE
KG	KILOGRAM
LVEDP	LEFT VENTRICULAR END DIASTOLIC PRESSURE
MAC	MINIMUM ALVEOLAR CONCENTRATION

MAP	MEAN ARTERIAL PRESSURE
MCG/ µG	MICROGRAM
MG	MILLIGRAM
MINS	MINUTES
MM HG	MILLIMETERS OF MERCURY
MOL	MOLE
NA	NORADRENALINE
NG	NANOGRAM
NIBP	NON-INVASIVE BLOOD PRESSURE
PKA	ACID DISSOCIATION CONSTANT
PO	POSTOPERATIVE
RPP	RATE-PRESSURE PRODUCT
RSS	RAMSAON SEDATION SCORE
SBP	SYSTOLIC BLOOD PRESSURE
$T_{½}$	HALF-LIFE
TD	TRIEGER-DOT
VAS	VISUAL ANALOG SCALE
VD	VOLUME OF DISTRIBUTION
α-2	ALPHA-2

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ABSTRACT

Introduction

Laryngoscopy and endotracheal intubation elicit reflex increases in heart rate and blood pressure, as well as cardiac rhythm irregularities. Clonidine premedication reduces the pressor response to laryngoscopy and intubation. The pineal gland releases the melatonin endogenously, which modulates sleep. This medicine has been utilized as premedication by several researchers in various dosing regimens.

Aim & Objectives

1. To demonstrate that oral melatonin reduces laryngoscopy and tracheal intubation's hemodynamic response.
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Material & Methods

- Our study was conducted at R. L. Jalappa Hospital and Research Centre, Tamaka, Kolar, in the Department of Anaesthesia. Study included 80 cases undergoing elective surgery under general anesthesia. These cases were divided into two groups of 40 each, using computer generated random numbers: Group M: Received 6 mg of melatonin, preoperatively 120 min before induction of anaesthesia and; Group C: Received 0.2 mg of clonidine, preoperatively 120 min before induction of anaesthesia. Baseline and Immediately after intubation and at 1,3,5 and 10 min following intubation -heart rate

(HR), systolic blood pressure, diastolic blood pressure, mean arterial pressure, and rate-pressure product were recorded. All the data was noted down in a pre-designed study proforma. Qualitative data was represented in the form of frequency and percentage and its association was assessed by Chi-Square test. Quantitative data was analysed between the two groups by using unpaired t-test if data passed 'Normality test' and by Mann-Whitney Test if data failed 'Normality test'. A p-value < 0.05 was taken as level of significance. Data was analysed using statistical software SPSS ver. 21.

Results

1. Present study has 56.3% females and 43.8% males, with comparable gender distribution in the study groups (p-0.367).
2. A total of 76.3% cases were in ASA grade I while 23.8% were in ASA grade II, with no variation across research groups (p -0.60).
3. Mean age and weight of the study group was 29.35 years and 61.6 Kg with no difference between study groups, respectively (p value of 0.09 and p value of 0.84).
4. Baseline heart rate, in both groups were comparable (78.1 vs 75.7 mins; p-0.50). Post induction, the heart rate fell in both groups ($p<0.01$) as compared to baseline. However, the fall was greater in melatonin group as compared to clonidine group ($p<0.01$). The heart rate increased in both groups post-intubation, but the rise was less in melatonin group as compared to clonidine group (p-value of 0.01)-statistically significant. Post-intubation until 10 mins, the mean heart rate was substantially lower in melatonin group ($p<0.01$).
5. At baseline, SBP, DBP, and MAP were compared in both the groups (p-value>0.05). Post induction, both groups showed fall in blood pressure as compared to baseline. Post-intubation, both groups recorded elevated blood pressure, but the rise was substantially

lower in melatonin group when compared to clonidine group ($p<0.01$). Post-intubation until 10 minutes, melatonin group showed significantly lower change in SBP (p-value<0.01).

6. In terms of mean RPP value at baseline, both groups were comparable (9203.7 vs 9061.3 mm Hg; p-0.73). Post induction, the RPP reduced in the both groups as compared to baseline (p-value<0.01). Post-intubation, RPP was less in melatonin and significantly more in clonidine group (p-value<0.01). Post-intubation until 10 minutes, the mean RPP was considerably higher in clonidine group (p-value<0.01).
7. Both groups didn't show any complications like hypotension, bradycardia and PONV during the procedure or post-operatively.

Conclusion

We observed that there was a considerable reduction in HR, SBP, DBP, MAP and RPP by both melatonin and clonidine. However, attenuation of both, pressor response to intubation was appreciable in melatonin than clonidine. This fall in HR and BP is mainly by the centrally mediated sympatholytic effect of the drugs. None of the cases experienced any adverse reactions like hypotension or bradycardia in both groups. We thus recommend use of oral melatonin for attenuating the hemodynamic response to laryngoscopy and intubation.

INTRODUCTION

Direct Laryngoscopy and intubation are aversive impulses that cause pressor responses such as rise in blood pressure and heart rate. [1]. In healthy people, this is less concern. However, those with diminished reserved cardiac function owing to coronary artery atherosclerosis, cardiac arrhythmias, congestive cardiac dysfunction, hypertensive disorders, cardiomyopathy, or advanced-age group are more vulnerable to the negative effects of these occurrences. [2]. As a result, steps must be taken to dampen these hemodynamic responses. These haemodynamic changes are caused by somatovisceral reflexes triggered by sympathetic activation. During endotracheal intubation, the sensory receptors of larynx and trachea are triggered, leading in the release of endogenous catecholamines, which cause increased heart rate & hypertension. [3].

There have been a number of medication regimens and procedures employed intermittently since the invention of direct laryngoscopy and tracheal intubation to reduce the severity of these stress reactions. Some of these medications include opioids, calcium channel blockers, sympatholytic drugs, β-antagonists, benzodiazepines, barbiturates & its derivatives, propofol, pregabalin and peripheral vasodilators [4]. Nevertheless, each medication has few limits, such as bradypnea, decreased BP, elevated & decreased heart rate, rebound hypertension, and hypersensitivity reactions. Consequently, there is always demand for a superior medication.

α-2 -Adrenoceptor agonist give an alternative to presently employed supplementary anaesthetic drugs due to their anaesthetic sparing and hemodynamic regulating properties. [5]. Clonidine is a central sympatholytic α-2 adrenoreceptor agonist. Clonidine premedication reduces the haemodynamic stress reactions to laryngoscopy and endotracheal intubation. Clonidine also lowers blood pressure by enhancing the sensitivity of the heart baroreceptor

reflex [6]. However, its limited selectivity for α-2 adrenoreceptors and extended half-life under anaesthesia have restricted its use.

Melatonin, or N-acetyl-5-methoxytryptamine, is a hormone endogenously released by the pineal gland that regulates sleep. Melatonin administered exogenously promotes sleep-onset and enhances sleep-quality. It differs from Benzodiazepines and its derivatives in that it induces a normal sleep-pattern without impairing cognitive processes. [7]. Adults and children have been premedicated with varying doses of this substance by a number of studies. It has mostly been investigated for decrease in pre operative anxiety , sedation, and pre operative mental and psychomotor functioning. [8,9]. However, it's role in reducing haemodynamic responses to direct laryngoscopy and tracheal intubation due to its inhibitory effects on the CNS, which is responsible for sedation and anxiolysis.

Considering above discussion, we have conducted this comparative research to assess hemodynamic responses of melatonin with clonidine given orally during direct laryngoscopy and endotracheal intubation.

AIM AND OBJECTIVES

1. To demonstrate that oral melatonin reduces laryngoscopy and tracheal intubation's hemodynamic response.
2. To demonstrate that oral clonidine reduces laryngoscopy and tracheal intubation's hemodynamic response.
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REVIEW OF LITERATURE

STRESS RESPONSE IN INTUBATION

Intubation is associated with tachycardia and hypertension. These circulatory responses following endotracheal intubation were described as stress response and is caused by reflex sympatho-adrenal stimulation. The stimulation of the oro-laryngopharynx elicits this sympathetic reaction.

Before discussing in detail about the stress response to intubation and laryngoscopy, its logical to understand the anatomy of the structure involved and physiological responses of the adrenoreceptors.

ANATOMY OF UPPER AIRWAY AND LARYNX ANATOMY [10]

Pharynx

The pharynx runs from the posterior portion of the nose at the base of the skull down to the level of the lower border of cricoid cartilage, where it joins the oesophagus posteriorly and the respiratory tract anteriorly through the larynx. The soft palate splits the pharynx into two sections: upper nasopharyngeal and lower oropharyngeal regions. The soft palate separates the pharynx partially into a) Nasopharyngeal b)oropharyngeal and c)laryngopharyngeal regions.

A)Nasopharynx

The pharynx is the area behind the nose, just above the soft palate. The roof and posterior wall create a continuous slope in opposition to the posterior portion of the body of the sphenoid, the basiocciput, and the atlas's anterior arch. The nasopharyngeal tonsil, also known as the adenoid, is a lymphoid tissue that sits under mucous membrane on the side of the nose opposite the basiocciput.

B) Oropharynx

Starting below the soft palate, it continues to the hyoid bone before continuing as the laryngopharynx at the level of epiglottis' upper border. The axis vertebra's body supports it from behind. The tonsillar pillars or fauces are located in oropharyngeal lateral walls. Glossopharyngeal and palatoglossal muscles are located in the anterior and posterior pillars, respectively.

C)Laryngopharynx

Laryngopharynx also known as hypopharynx is located behind the larynx. It stretches from the epiglottis' top border to the cricoid cartilage's lower border. The lateral wall has two piriform fossae's, one on either side of the laryngeal opening.

The aryepiglottic fold forms the medial boundary of the fossa, while the thyroid cartilage & thyrohyoid membrane define the lateral boundary. The internal laryngeal nerve is located beneath the mucosa of the fossa. Potential nerve injury occurs during removal of foreign bodies from the piriform fossa.

TONGUE

The tongue is a strong muscular organ near the base of the mouth. It consists of an oral portion located in the mouth & a pharyngeal portion situated in the pharynx. Sulcus terminalis is a V-shaped sulcus that separates the oral and pharyngeal cavities.

- **Oral region:** Positioned on the mouth's floor. The margins are free and in touch with the gingiva and teeth.
- **Pharyngeal region:** Folds of mucous membrane link the posterior portion of the tongue to the epiglottis. Both the medial and lateral glossoepiglottic folds may be seen here. A pouch termed vallecula can be seen on each side of the median fold. The vallecula & piriform fossa are separated by the lateral folds.

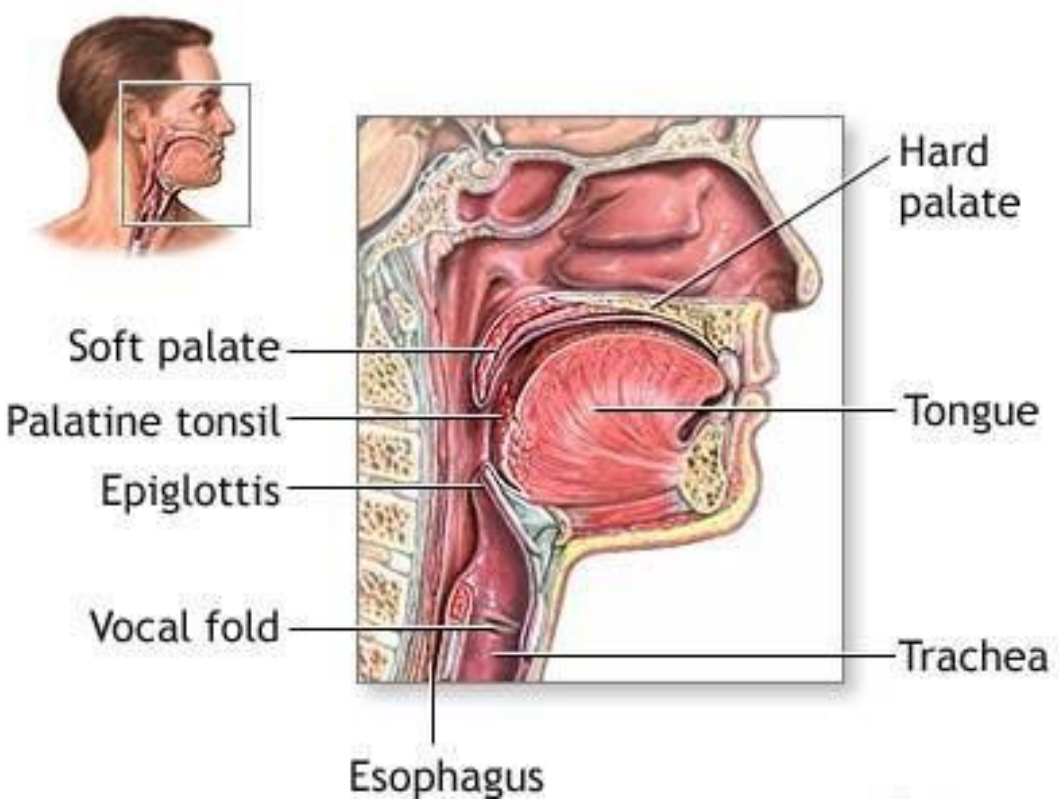

Figure 1: Upper airway anatomy

LARYNX

Organ for production of voice. It is situated at the crossroads between the food and air passageways. The larynx is located near the neck's anterior midline. It runs from the base of the tongue to the base of the cricoid cartilage. It is located in front of the third, fourth, fifth, and sixth cervical vertebrae in adult males. However, it is situated little higher in children and adult females. There are no variations in laryngeal size between males and girls until adolescence. When adolescents reach puberty, the larynx of males grows more quickly than that of females. In females, larynx is cephalad & smaller. Anteriorly, the opening to the larynx is confined by the top border of the epiglottis, posteriorly by a fold of mucous membrane extended in between two arytenoid cartilages, and laterally by aryepiglottic folds. The cartilaginous framework of the larynx is held together by joints, ligaments, & membranes. Numerous muscles move this cartilaginous framework.

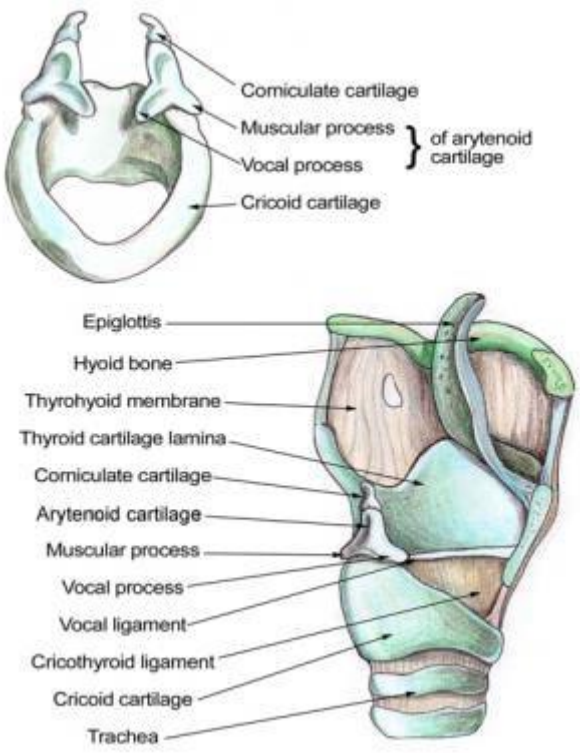

Figure 2. Anatomy of Larynx

Nerve Supply

Branches of vagus nerve, superior and recurrent laryngeal nerves innervate the larynx.

Pharyngeal autonomic innervations

"The superior cervical ganglion's laryngo-pharyngeal branches nourish the carotid body and proceed to the sides of the pharynx, where they connect with branches from the glossopharyngeal & vagal nerves to create the pharyngeal plexus. Pharyngeal-plexus, which is formed by the branches of the glossopharyngeal, vagal, & sympathetic (from the superior cervical ganglia) nerves, provides nerve supply to the pharynx. Glossopharyngeal and vagal are the principal sensory nerves, with branches of the maxillary nerve supplying much of the mucous membrane of the nasal section of the pharynx. The smaller palatine and glossopharyngeal nerves supply the mucous membrane of the soft palate".

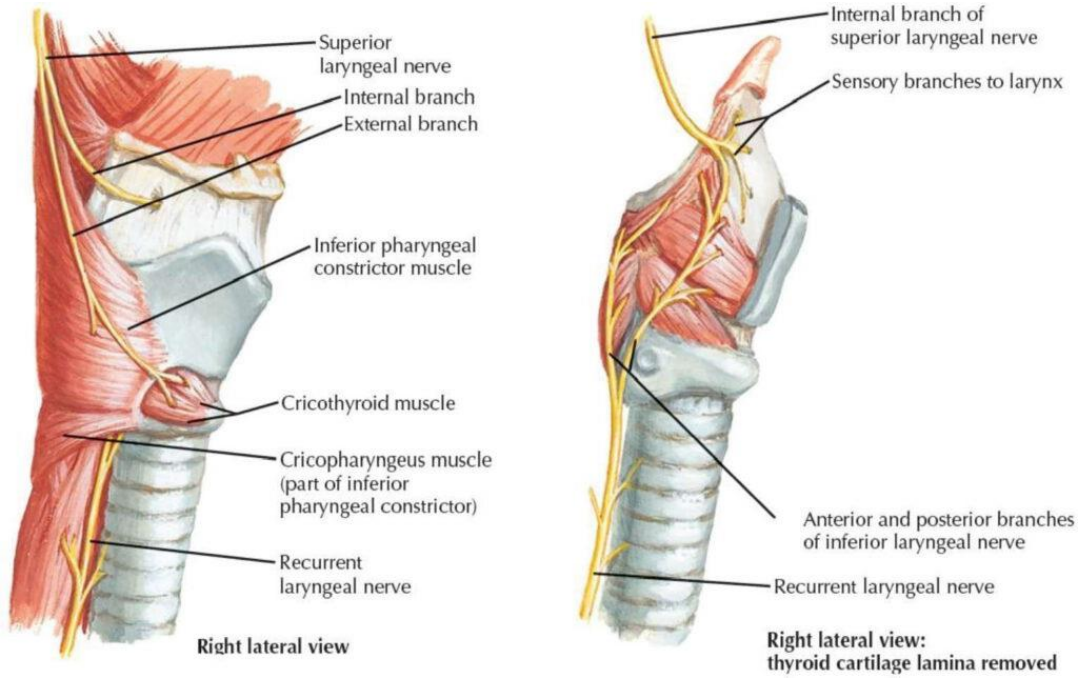

Figure 3. Nerve Supply of Larynx

PHYSIOLOGY OF ADRENORECEPTORS

The α-2 receptors can be located in a variety of locations all through the body. They are found in peripheral nervous system and central nervous system, in tissues of renal system, hepatic system, pancreas, eye, smooth muscles of vascular system and platelets [11]. The wide range of effects mediated by alpha-2 adrenoceptors can be explained by the fact that their physiological responses are site-specific. [12].

These receptors are located in pre-synaptic, post-synaptic, and extra-synaptic regions, which makes the categorization of α-2 receptors based on anatomical location complex. [13]. They are categorised into three distinct subtypes, each of which performs a specific function in the α-2 receptor system. The predominant subtype A is in CNS, is responsible for sedation, analgesia and sympatholytic effect. Subtype B, located predominantly in the peripheral vessels, is responsible for transient elevation of blood pressure. Subtype C, located in Central Nervous System, is responsible for anxiolysis [14].

The impact of the αlpha-2 adrenergic receptor is mediated through activation of the

GNRP (G-proteins). The inhibition of adenylate-cyclase, which leads to a reduction in synthesis of 3,5-c-AMP, is one way in which active G-proteins regulate cellular activity via the second messenger system. This causes hyperpolarization of membranes of excitable cell and serves as an efficient technique of inhibiting neuronal activation. This inhibition of neurotransmitter production may be due to the fact that alpha-2 receptor stimulation reduces calcium entrance into the nerve terminal. [15].

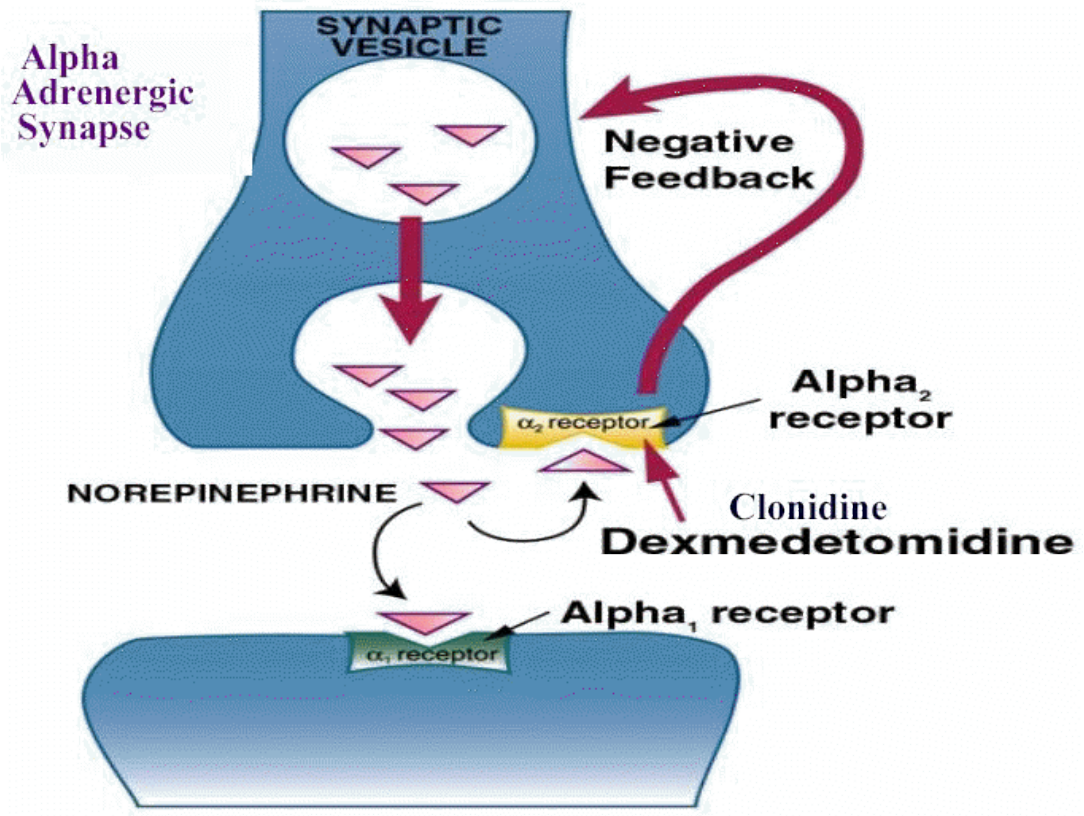

Figure 4. α_2 adrenergic receptor

PHYSIOLOGY OF STRESS RESPONSE

The internal biological environment of the body is maintained by the autonomic nerve system. The sympathetic-adrenal system governs the body's stress response. The sympathetic-adrenal system neurotransmitters are noradrenaline & adrenaline. The adrenal medulla's normal, baseline production of adrenaline, at 0.2 mcg/kg/min, & noradrenaline, at 0.05 mcg/kg/min, is sufficient to sustain normal human physiology. The hypothalamus triggers an increase in catecholamine release in the body under stressful events by activating

the sympathetic nervous system and the adrenal glands. This response is highly connected with the endocrine system's role in stress management.

The pressor reaction to direct laryngoscopy & endotracheal intubation is recognized to be a sympathetic reflex triggered by epipharyngeal and laryngeal stimulation. Tomori and Widdicombe JF et al. investigated the impact of stimulation at various places in the respiratory system on systemic blood pressure in paralysed cats. [16].

The epi-pharyngeal area elicited the greatest blood pressure rise, whereas the tracheobronchial tree produced the least. Stimulation of all the sites of the respiratory tract enhanced frequency of discharge of the efferent cervical sympathetic fibers. For epi-pharyngeal and laryngeal stimulation, they showed statistical significance. In the same study, it was shown that there is bronchodilation on stimulation of the nose and epipharynx and bronchoconstriction on stimulation of larynx.

Russell WJ, Morris RG. et al. [17] stated that BP & Noradrenaline levels in blood were dramatically elevated during intubation, although plasma adrenaline and dopamine concentrations did not alter appreciably. Successful results were reported following ganglionic alpha and beta adrenergic blockers.

Reid LC, Brace DE.et al [18] concluded that both the afferent and efferent channels of the reflex were considered vagal-origin, cardiac reflexes might begin in the tracheo-bronchial tree or larynx and cause a response by a rapid rise in vagal tone.

The vagus nerve acts as the afferent arm of the reflex arc and provides sensation to the tongue base, epiglottis, & trachea. The effector system is less clearly defined. Probably the effect is seen due to the stimulation of the cardio acceleratory fibers which implies that there is an increment in tone of sympathetic system rather than parasympathetic tone.

This reflex circulatory response appears to be independent of the anaesthetic agents used. The depth of anaesthesia obtained is the more important factor. The changes are

exaggerated by straining, coughing on the endotracheal tube and Hypercarbia.

The type of blade used for laryngoscopy determines the grade of autonomic response to laryngoscopy. In theory, blind nasal intubation may cause less of pressor response as laryngoscopy is avoided. Laryngoscopy in addition to pressor response could cause arrhythmias.

The reason for increase in blood pressure is difficult to evaluate. There may be increase in heart rate during laryngoscopy which is due to cardioacceleratory action.

Rate pressure product is the best index for myocardial oxygen consumption. Gerola and his colleagues introduced this idea [19]. In individuals with CAD, the RPP should not exceed 12,000 to prevent intraoperative myocardial ischemia.

The majority of the arrhythmias induced were sinus arrhythmias. Others included sinus bradycardia, nodal rhythm, ventricular tachycardia, premature ventricular beats, and fibrillation.

Tracheal intubation activates the ANS as well as the CNS, as demonstrated by an increase in EEG activity and BMR. In patients with reduced intracranial compliance, a rise in CBF may lead to increased ICP, which may cause herniation of brain tissue and significant neurologic deterioration.

Laryngoscopy and its consequences should be distinguished from the procedure of inserting an endotracheal tube into the trachea in order to separate the circulatory alterations and catecholamine release into two phases (or of a catheter or bronchoscope). Without intubation, laryngoscopy alone causes a supraglottic pressure stimulus that significantly elevates both systolic and diastolic pressures [18] above pre-induction control levels and from a stable anaesthetic state's central level. The minor and insignificant increases in heart rate caused by laryngoscopy alone are not concerning.

The act of intubation, which involves inserting an endotracheal tube into the trachea or inserting a catheter, activates infraglottic receptors, which in turn causes an extra cardiovascular response and an increase in catecholamines. The pressor response has significantly increased from pre-induction control levels, rising by 36%. In addition, tracheal intubation now dramatically raises heart rate by roughly 20%, but laryngoscopy alone has minimal effect on heart rate, as was previously mentioned.

Patients with heart disease may experience a number of difficulties from the endocrine neural response to tracheal intubation that results in elevated HR & BP. Myocardial ischemia in patients with insufficiency in coronary arteries is the most known adverse issue in cardiovascular system related with intubation.

Heart rate & blood pressure are the two main things that influence how much oxygen the myocardium needs, therefore when tracheal intubation produces a significant rise in both, the myocardial oxygen demand must be increased in order to give more oxygen-rich blood through the coronary circulation. The capacity to enhance myocardial oxygen supply at peak time is minimal when one or perhaps more occlusive coronary defects cause relatively constant coronary blood flow, & an unexpected surge in cardiac demand causes ischemia in cardiac tissue that may result to dysfunction in myocardium or overt infarction in tissue.

Additionally, a rise in LVEDP may exacerbate ischemia brought on by arterial hypertension, further impairing the perfusion of subendocardial tissue.

ST segment depressive episodes in the EKG & augmented pulmonary-artery diastolic pressure in atherosclerosed individuals are brought on by these conditions. These incidents could sometimes raise the risk of perioperative myocardial infarction.

During endotracheal intubation, patients who have vascular defects that compromised the endothelium of major arteries are at danger. Transmural pressure plays critical role in the integration of cerebral & aortic aneurysms; a rapid rise in blood pressure can cause in a

ruptured vessel & a sharp deterioration in the patient's condition. The anesthesiologists must replace a substantial amount of blood as a result, and the surgeon faces additional technical challenges while attempting to examine the lesion and put a vascular prosthesis.

PHARMACOLOGY OF CLONIDINE [20]

A direct acting alpha-2 agonist called clonidine has historically been administered as an antihypertensive medication. In addition to having an antihypertensive impact, clonidine has recently shown to be a potent sedative & analgesic that, when used as part of an anaesthetic approach, lowers the amount of anaesthetic drugs needed. Therefore, it is appropriate to reevaluate potential novel uses for clonidine in clinical anaesthesia.

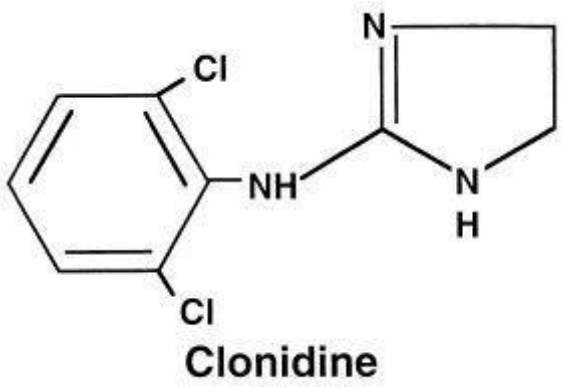

Figure 5. Clonidine Structure

N – (2,6 – dichlorophenyl) -4,5 –dihydro – 1H – imidazol – z – amine.

PHARMACODYNAMICS

α-2 adrenoreceptors are found on primary afferent terminals (both peripheral and spinal endings), neurons in the spinal cord's superficial laminae, and within multiple brainstem nuclei associated in analgesia, indicating the possibility of analgesic action at peripheral, spinal, and brainstem sites. In contrast to blood, there is a high association between clonidine concentration and analgesia following clonidine treatment in cerebrospinal fluid (CSF). After

epidural administration, clonidine is quickly absorbed into the spinal CSF compartment, with concentrations peaking 30-60 minutes later. Clonidine's site of action for analgesia is certainly not the cerebrospinal fluid, and the medication can reach locations providing analgesic effect in the spinal cord or anywhere.

Clonidine, like other lipid-soluble medications, can provide analgesia by administering perorally or intravenously, epidurally, or intrathecal injection. Nevertheless, clonidine is more effective when administered neuraxially as opposed to systemically, suggesting a spinal site of action. This action of clonidine on alpha2-adrenoreceptors has been showcased by partial reverse of epidural clonidine analgesia & sedation by administering the α-2 adrenergic blocker, yohimbine although the effects on BP & HR were unaffected.

There are also suggestions that (in animal studies) clonidine causes analgesia, in part, by spinal cholinergic activation due to increase in acetylcholine concentrations in the dorsal more than ventral horn of spinal cord. Inhibition of substance P release is also thought to have role in analgesia. Clonidine also enhances blockade of sensory & motor activity from epidural injection or peripheral nerve block injection of local anaesthetics. Several alternative processes have been proposed. First, Clonidine's capacity to modify the activity of potassium channels in isolated neurons in vitro (Hyperpolarization of cell membranes occurs) may be the mechanism by which it reduces anaesthetic needs significantly. Second, in therapeutic settings, clonidine may produce significant local vasoconstriction, limiting vascular clearance of the local anaesthetic; however, there is limited evidence for this mechanism at clinically employed doses.

Clonidine's sedative effect is caused by its activities on the locus ceruleus. Sedation following epidural clonidine is most likely the result of systemic absorption and circulatory redistribution to higher locations. The quality of sedation generated by alpha 2 agonists differs from that produced by medications that act on GABA receptors (Midazolam,

Propofol). Clonidine acting on alpha2- adrenergic receptors inhibits the sleep regulatory physiological processes in locus ceruleus via a G-protein coupled mechanism and produces sedation. The consequence is a peaceful patient who can be readily awakened to full awareness. Medications that stimulate gamma-aminobutyric acid receptors can induce a clouding of consciousness & paradoxical agitation, in addition to resistance and dependency.

Clonidine provides dose-dependent drowsiness across the dosage range of 50 to 900µg with quick onset (200min) independent of mode of administration. Sedation is severe for 4-6 hours after a high epidural bolus dosage (700mcg). Sedation is a desirable quality in many circumstances, and multiple studies have shown that when clonidine is delivered intraoperatively, the requirement for other sedatives and anxiolytic drugs is minimised.

Clonidine has a complicated effect on blood pressure following neuraxial or systemic delivery due to competing activities at different locations. Activation of postsynaptic alpha-2 adrenergic receptors in the nucleus tractus solitarius and locus ceruleus of the brainstem lowers sympathetic activity. It also stimulates non-adrenergic imidazoline, favouring binding sites in the lateral reticular nucleus, resulting in hypotension and an anti - arrhythmic effect. In the periphery, its activity on presynaptic alpha-2 adrenoceptors at sympathetic endings reduces norepinephrine release, resulting in vasodilation & decreased chronotropic urge. These brainstem & peripheral actions of alpha-2 adrenergic receptor stimulation are balanced by direct peripheral vasoconstriction caused by circulating clonidine's action on alpha-1 adrenoceptors. As a result, the dose-response curve for clonidine administered by neuraxial or systemic routes is U-shaped, with peripheral vasoconstriction from high circulating drug concentrations countering central sympatholytic activity. Clonidine neuraxial injection acts by blocking sympathetic pre-ganglionic neurons in the spinal cord, in addition to the brainstem and peripheral sites of action. Intrathecally administered alpha-2 adrenergic receptor agonists' influence on hemodynamic parameters is further complicated by the

segmental site of injection, the patient's posture, the pace of injection, and the temperature of the injected solution. Furthermore, combining alpha-2 adrenergic receptor agonists with local anesthetic drugs may enhance the extent of sympatholytic activity &, as a result, hypotension. Clinical investigations in surgical patients, on the other hand, have very occasionally demonstrated greater decreases in arterial blood pressure or heart rate in patients who received both intrathecal clonidine and local anesthesia. [21].

Clonidine reduces heart rate by two mechanisms:- presynaptic norepinephrine inhibition and vagomimetic effect.

Clonidine's hemodynamic effects begin after 30 mins of neuraxial or systemic delivery, peak within 1-2 hours, and persist roughly 6-8 hours following a single injection. Clonidine, alone or in combination, has not been associated with a delayed onset of hypotension. Even after higher doses, alpha-2 adrenergic agonists like clonidine don't cause substantial respiratory depression, nor do they aggravate opioid-induced respiratory depression. [21].

PHARMACOKINETICS [22]

- Since clonidine is extremely lipid soluble, it is quickly absorbed when administered orally, intravenously, or epidurally. Following epidural injection, clonidine is rapidly and extensively distributed into the spinal CSF compartment, with a peak concentration occurring 30-60 mins later. Following epidural clonidine treatment, there is a significant association between concentration of clonidine in the CSF & analgesia. Clonidine is easily absorbable from epidural veins into the bloodstream and reaches concentrations in the body (0.5-2 ng/ml) that are linked to a hypotension mediated by the CNS. After being administered intravenously, it is easily absorbed extra vascularly , such as the CNS.
- Molecular weight: 230.093 gm / ml

- Bio-availability: 75-95%
- Protein-binding: 20-40%
- Vd : 2.1 + 0.4 L/Kg
- Elimination half-life (T ½): 9 + 2 hours
- Onset time: 26 + 11 mins

Clonidine is hydroxylated in the liver to produce the main metabolite, p-hydroxyclonidine. The liver can only process 50% of the medicine, leaving the other 50% to be eliminated in the urine unchanged. The most significant protein binding site for clonidine in vitro ranges from 20 to 40% of plasma albumin [23].

SIDE EFFECTS [23]

Clonidine's most frequent side effects include sleepiness, dry mouth, bradycardia, and hypotension. It also prevents women from having orgasms. Following abruptly stopping clonidine therapy (1.2 mg/day), rebound hypertension can develop as early as 8 hrs & as long as 36 hrs after the previous dosage. Resuming clonidine medication or using a vasodilator such hydralazine or sodium nitroprusside can usually control rebound hypertension.

ANAESTHETIC USE OF CLONIDINE [24]

1. Premedicating: When Clonidine is used as a premedicant, the sedative effect may be beneficial. Additionally, it has a sparing impact on anaesthesia. Both the dosage of intravenous hypnotics and the MAC of volatile anaesthetic drugs are decreased by alpha-2 adrenergic agonists. It is advised to administer clonidine at doses of 4 mcg/kg orally or intranasally, and 5 g/kg rectally for sufficient sedation. When used as a premedicant, it can be especially helpful for patients who fall into certain subgroups, such as drug users and

alcoholics who experience withdrawal symptoms, palliative care patients and those with chronic pain and people with hypertension

2. Control of hemodynamic response: Alpha-2 adrenergic agonists have central and peripheral effects on hemodynamics. The lateral horn of thoracic spinal cord's presynaptic sympathetic neurons are also suppressed by alpha-2 adrenergic agonists. It should be emphasised that the local application of the cholinesterase inhibitor neostigmine reverses this effect. During surgical stimulation, laryngoscopy, and intubation as well as other procedures, clonidine inhibits hypertension and tachycardia.

Postoperative analgesia and Regional Anaesthesia

Clonidine increases the analgesic effect of opiates and interacts with cholinergic neurons to do so. They increase the duration of local anaesthetic blocking.

Central Neuraxial Blocks:

A. Epidural: If administered as the only medication to generate epidural analgesia, high doses (up to 2–3000 mcg/day) are required to produce long-lasting analgesia. Significant drowsiness, bradycardia, and hypotension are frequent at these doses. This makes its use as a sole quite uncommon. It is more frequently combined with opioids, local anaesthetics, or both to deliver good to outstanding analgesia with few adverse effects. The dose is restricted to 10–15 mcg/hour when used in conjunction with other medications.

B. Spinal: A shorter-lasting analgesia is produced by clonidine in the spinal region, but there is no risk of respiratory depression or urine retention. Intrathecal Clonidine can be given at a maximum dose of 1-2 mcg/kg. When combined with local anaesthetics, Clonidine lessens tourniquet pain during lower limb surgery, improves the block's quality and span, & stops shivering.

C. Caudal: When given along with local anaesthesia, caudal Clonidine can lengthen sedation & analgesia by two or three-fold without having an adverse effect on hemodynamics. The

suggested dosage for caudal administration is 1-2 mcg/kg.

Additionally recommended for use in labour analgesia is epidural clonidine. Sufentanil, bupivacaine, and clonidine have all been administered either singly or in combination. Although clonidine does pass the placental barrier, there have been no reported negative effects on babies. The indicated dose of clonidine during labour is 100 mcg in order to prevent hypotension and bradycardia in the foetus as well.

Blocks in Peripheral Nerves

In peripheral nerve blocks, the clonidine is frequently utilized as an adjunct to local anaesthetic drugs to prolong the time of anaesthesia and analgesia. This action is produced at doses of just 2 to 3 mcg/kg, which obviously lowers the likelihood of adverse consequences.

Contraindications

Contraindications include medication hypersensitivity, infection at the injection site for the epidural, and bleeding issues (epidural use)

Dosage recommendations [25]

- Epidural: 1g/kg (or) 50g.30g/hr
- Intrathecal: 15g to 30g
- Oral: 3-5g/Kg
- Intravenous: 50–75 mg (or 1gm/kg) 15 mins prior to induction to mitigate intubation response; hypertensive crisis: 150–300 mg (or 3gm/kg); shivering management :30 mg administered.

REVIEW STUDIES ON CLONIDINE

Raval D et al. [26] performed research on 100 participants, ASA Grade 1 & 2 patients were selected ranging 18 to 65 years to interpret the effects of peroral clonidine, a placebo, and

oral diazepam as premedications. The patients were split into three groups, with 20 participants in the placebo group & 40 participants each in clonidine and diazepam groups. In contrast to diazepam, oral clonidine induced less sedation and the same degree of anxiolysis, but more pronounced sedation, greater anxiolysis, and a good antisialogogue effect. It also suppressed the haemodynamic reactions during direct laryngoscopy & endotracheal intubation. In a randomised, double blind research including 69 normotensive patients, Wright PM et al. [27] found that using oral clonidine as a routine premedicant resulted in a considerable decrease in anxiety, appropriate sedation, and a reduction in the amount of methohexitone needed to induce sleep. The effects of intubation-induced tachycardia were also reduced by clonidine. Without causing hypotension, a lower dose of the alpha 2 adrenergic agonist may be beneficial in lowering anxiety and terror. Carabine UA et al. evaluated 80 female patients with normal blood pressure. In a double-blind, randomised trial [28] comparing oral clonidine dosages of 100 mcg, 200 mcg, & 300 mcg with a conventional benzodiazepine premedicant, it was found that oral clonidine 200 mcg significantly reduced nervousness and improved the quality of anaesthesia induction when compared to the other groups. Clonidine also caused a reduction in HR & arterial pressure. After premedication with clonidine 300 mcg, hypotension lasted into the postoperatively; hence, this dose is not advised as a regular premedicant.

In a research by Tanaka M et al. [29], oral clonidine administered 30 to 90 mins prior to surgery attenuates the hemodynamic reactions to tracheal intubation, decreases anaesthetic doses, and also reduces the need for opioids.

In a research by Ghignone M et al. [30], oral clonidine 5 g/kg 90 minutes before induction of anaesthesia lowers the need for fentanyl by 45% compared to the usual premedication group.

According to research by Martina A. et al. [31], premedication with intramuscular

clonidine dose of 4.5 gm/kg reduced the beta endorphin immunoreactivity-based haemodynamic response to endotracheal intubation.

Studies by Batra YK et al. [32] and Sukanya M et al. [33] suggested that oral clonidine may be effective in reducing the increase in HR & BP brought on by direct laryngoscopy & intubation during a typical induction sequence.

According to a research by Chadha R et al. [34], oral clonidine pretreatment can successfully alleviate haemodynamic instability, such as tachycardia and hypertension brought on by laryngoscopy during craniotomy. Additionally, they discovered that thiopental's sleep dosage was decreased following clonidine pretreatment.

To examine the effectiveness & safety of peroral clonidine & peroral pregabalin as a premedication to mitigate hemodynamic response in patients having cholecystectomy through laparoscopy, Parveen S et al. conducted research [35]. Both oral pregabalin 150milligram & oral clonidine 300mcg were successful in reducing the haemodynamic reaction to direct laryngoscopy and endotracheal intubation. In the study it was noted that the reduction in heart rate and blood pressure after laryngoscopy, were better with clonidine than pregabalin. Additionally, we discovered decrease in HR was frequent with both medications, more evident in clonidine group. Pregabalin group had better post-operative analgesia than clonidine group. Both medications sedate you, but pregabalin causes it more so.

Fentanyl and clonidine were compared by Sameenakousar M et al. for attenuating the stress response [36]. The increase in HR was 48.07% in control group, while it was substantially low (20.75% and 12.57%, respectively) in the fentanyl (II) and clonidine (III) groups (p0.001). The highest reading in systolic blood pressure in the control group was noted 5 minutes (42.62%), or after the laryngoscopy and intubation. Over the course of ten minutes, it gradually fell (17.39%). The largest rise over the preinduction value with the administration of fentanyl was 9.91%, but in the group receiving clonidine, it was only

7.38%. Both displayed a significant suppression (P.001) as compared to the control, with clonidine producing the superior outcomes. The greatest increment in DBP was observed at 5 minutes in control group and was 30.12% in the both groups, respectively, with the clonidine group performing better (P.001).

The efficiency of peroral clonidine & i.v lignocaine as a premedication to attenuate the stress reaction due to such required movements was compared by Roy S et al. [37] in their study. Within the initial crucial 10 minutes following intubation, Group C showed statistically significantly greater mitigation of SBP,DBP,MAP & HR than did Group L.

Jehangir Allam et al. [38] investigated how oral clonidine affected hemodynamic alterations brought on by laryngoscopy, intubation, and the stress reaction associated with surgical procedures. In both groups, there was a statistically significant difference in HR, SBP, DBP, MAP & RPP. Hemodynamic variables were more consistently steady in the clonidine group.

The effectiveness of peroral Clonidine versus Pregabalin as premedication was assessed by Khan AA et al. [39]. Along with delivering beneficial pre-operative anxiolysis & sedation, peroral clonidine (300mcg) administered 2hrs prior to induction was beneficial in mitigating the hemodynamic stress to laryngoscopy and intubation. Although oral pregabalin (75 mg) provided a significant amount of anxiolysis and very slight drowsiness compared to placebo, it was ineffective in reducing the hemodynamic stress response to intubation. The parameters of recovery are not statistically significantly among the groups. None of the planned patients experienced any surgical complications.

Oral Clonidine premedication was evaluated by Arshi K et al. [40] for attenuating the hemodynamic reaction to direct laryngoscopy and intubation. According to a research, clonidine reduces anxiety, HR, SBP, DBP & MAP after 90 minutes. In the study to determine if clonidine can prevent an elevation of SBP & HR after intubation, the clonidine group

significantly outperformed the placebo group.

Research by Mohammadi SS et al. [41] compared the effects of lidocaine and clonidine on pressor reactions to tracheal intubation & laryngoscopy in controlled hypertension participants receiving general anaesthesia. Hemodynamic measures, including HR, SBP, DBP & MAP at the assessed points, did not show difference significantly among the two groups. Additionally, there were no notable variations in stress responses at the assessed points within any group (P-value > 0.05). Three participants in lidocaine group & twenty individuals on clonidine both reported having dry mouths (P = 0.001). Bradycardia was present in 14 patients receiving clonidine and 4 patients receiving lidocaine (P = 0.008). Orthostatic hypotension was present in six patients receiving lidocaine and 19 patients receiving clonidine (P = 0.002).

To compare the effectiveness of peroral clonidine vs peroral pregabalin as premedication to obtund hemodynamic interaction in patients underwent surgeries electively, Murari T et al. [42] conducted a study. Mean (standard-deviation) Heart rate, SBP, DBP, and Mean arterial Pressure in both groups did not significantly differ at baseline (p>0.05). Before induction and at the intervals of 1, 3, 5, 10, and 15 minutes, group A's mean (SD) HR was considerably decreased than group-B (p-value<0.05). In comparison to group B, group A's mean (SD) SBP and MBP were lower prior to induction, quickly following intubation and at 1st, 3rd, & 5th min (p-value<0.05). Before induction, group A's mean (SD) DBP was substantially lower than that of group-B. (p-value 0.012). Nonetheless, the pregabalin group had greater post-operative analgesia. Pregabalin use increased sedation whereas clonidine use increased bradycardia.

A prospective, randomised, double-blind trial was undertaken by Upendra Kumar S et al. [43] with 60 patients between the ages of 15 and 65 who were ASA I and II category. In each group, there were 30 patients. 90 minutes prior to surgery, Group A got peroral

clonidine 5g/kg & Group-B administered peroral gabapentin 800mg. Laryngoscopy was done after induction. Following the development of the direct laryngoscope At 0, 1, 3, 5, 10, 15, and 30 minutes during the laryngoscopy, the patient's HR, SBP, DBP, & MAP were all assessed. In all groups, it was seen that the pulse rate declined at 0 and 1 minutes, climbed at 3 minutes, and steadily decreased by 30 minutes. At all times, Group A had superior pulse rate control than Group B, and at 1 and 3 minutes, this difference was statistically significant. In both groups, MAP was lower than baseline at all times but for the third minute. Except at 15 & 30 mins, none of the group showed statistically significance difference, despite the decrease appearing to be greater in Group A over Group B. Additionally, except for the third minute, both groups' SBP and DBP decreased from baseline at all periods. Statistics did not support the difference. They came to the conclusion that peroral gabapentin 800 mg & oral clonidine 5 g/kg given 90 mins prior to surgery both significantly lessen the hemodynamic pressor response to direct laryngoscopy. They also highlighted that compared to clonidine, gabapentin generates higher postoperative sedation.

In order to ascertain the effects of peroral clonidine as a premedicant on sedation, anxiolytic, & stress reactions during the immediate preoperative period, laryngoscopy, intubation, & in post anaesthesia recovery, Laurito CE et al. [44] undertook a study. A randomised double-blind trial involving 40 persons with ASA physical status I and II was done. Four groups were created for the patients (clonidine 100 mcg, clonidine 200 mcg, triazolam0.25 mg, or placebo). At the moment of therapy, 90 minutes later, as well as right before induction, anxiety & sedation levels were noted using an ordinal scale. To guarantee a strong stress response, hemodynamic monitoring was performed at 1-minute intervals and 45 seconds following laryngoscopy. They came to the conclusion that 200mcg of oral clonidine were beneficial in lowering preoperative behavioural and hemodynamic responses as well as in reducing systolic hypertension brought on by extended laryngoscopy.

To assess peroral clonidine vs gabapentin as a premedicator for mitigating stress response to direct laryngoscopy & tracheal intubation, Singhal SK et al. [45] conducted a randomised research. Patients were categorized into 2 groups at random. Clonidine 200mcg was given to group A, whereas oral gabapentin 900mg was given to group B. 90 minutes before induction, medications were given. They came to the conclusion that oral clonidine 200 mg, given 90 minutes before anaesthesia, offers better hemodynamic response attenuation to direct laryngoscopy & intubation than oral gabapentin 900 mg, which also attenuated the hypertensive reaction fairly but did not attenuate the tachycardic response. When compared to gabapentin, clonidine also offered better sedation and anxiolysis.

R Sharma et al. [46] conducted a randomised-trial to evaluate the impact of peroral clonidine premedication on stress response after electroconvulsive 25 therapy. 25 patients with ASA 1 and 2 physical status who were planned for Electroconvulsive therapy were included in this study. They ranged in age from 20 to 50 and in weight from 50 to 70 kg. Each patient was given 300 mcg of clonidine or a placebo 90 mins before receiving ECT. Baseline Immediately prior to attaching the intravenous cannula, the patient's HR, SBP, DBP & MAP were noted. The same characteristics were recorded following induction, immediately following the delivery of the electric shock that ended the seizure, and every minute for 10 minutes. He came to the conclusion that peroral clonidine (300 mcg) reduces the initial hypertensive reaction following ECT, but this antihypertensive impact was only made possible by lowering BP beforehand.

In order to compare peroral gabapentin, pregabalin, & clonidine as premedications for anxiolysis, sedation, and mitigation of hemodynamic reaction to intubation, Waikar et al. [47] conducted a randomised prospective two way-blind study in 90 patients of ASA garde 1 & 2 in between 18 and 60 yrs. Participants were categorised into 3 groups at random. Preoperative medication was given 90 minutes before the procedure. Pregabalin 150 mg was given to

Group A, gabapentin 900 mg to Group B, and clonidine 200 mcg to Group C. In their investigation, it was found that clonidine reduced mean HR showed statistical difference at both 5 & 10 mins post intubation. At 1 min and 3 minutes post intubation, the mean blood pressure was considerably lower while taking pregabalin. In all the groups, the sedation and anxiety scores were statistically significant, although pregabalin increased their statistical significance.

PHARMACOLOGY OF MELATONIN [48]

In 1958, melatonin was discovered. The chemical structure is C13H16N2O2. It has a molecular mass of 232.28 g/mol. All significant taxa of organisms naturally contain melatonin. In all animals and vertebrates, the pineal gland is where it is mostly synthesised. It secretes more at night and less throughout the day. Melatonin is produced in peripheral tissues & other organs using tryptophan.

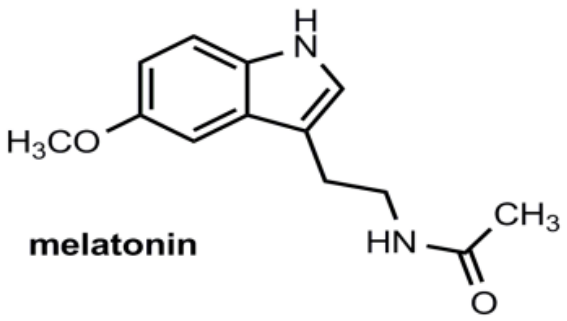

Figure 6. Chemical structure of Melatonin

Pharmacokinetics

Depending on the melatonin phase response curve in humans, small doses (300 mcg) of melatonin administered several hours before sleep move the biological clock earlier, favouring faster sleep onset and arising in the morning. Following intravenous injection, melatonin is quickly disseminated & removed. Plasma concentration rises after oral dosing

and is then eliminated in 60 mins. The $t_{½}$ of melatonin is around 35 and 50 minutes. 90% of exogenous melatonin taken orally is eliminated from liver in humans. A minor sum is also lost in urine & discovered in saliva. Melatonin has a bioavailability of between 10% and 50%. The cyt-P450 enzyme subtype CYP1A2 converts melatonin to 6-hydroxymelatonin in the liver. For excretion in the urine, metabolites are complexed with glucuronic or sulfuric acid. Melatonin is unaltered medication discharged in urine in amounts of 5%. Cyclic 3-hydroxymelatonin, n-acetyl-N2-formyl-5-methoxy kynuramine(AFMK), & n1-acetyl-5-methoxykynuramine(AMK) are a few of the metabolites created when melatonin reacts with a free radical [49].

Pharmacodynamics

Melatonin is a complete agonist of the G protein coupled receptors (GPCRs) melatonin receptors 1 (picomolar binding affinity) & 2 (nanomolar binding affinity), these receptors are found in humans. Although melatonin receptor-1 is Gq coupled, melatonin receptors 1 & 2 are both Gi/o - coupled G protein coupled receptors (GPCRs). By signalling through melatonin receptors, Melatonin also acts as a powerful free radical scavenger in the mitochondria, which encourages the development of anti-oxidant enzymes like superoxide-dismutase, glutathione-peroxidase, glutathione-reductase, & catalase.

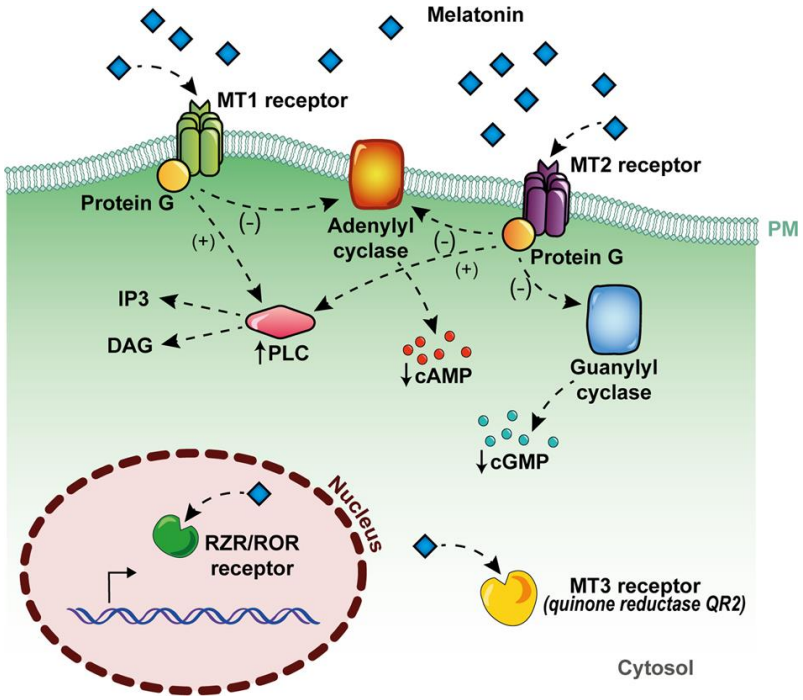

Figure 7. Mechanisms of action of melatonin

Melatonin can exert its effects by acting through receptor-independent mechanisms, which involve the direct interaction of melatonin and other molecules, and they are mainly related to its antioxidant and radical scavenging action (a). As any other hormone, melatonin can also act through specific cellular receptors, by membrane melatonin receptors, called MT1 and MT2, which are seven transmembrane-spanning proteins belonging to the G-protein-coupled receptor (GPCR) superfamily, by the cytosolic enzyme QR2 (also called MT3), or through the nuclear receptors RZR/ROR (b)

DOSAGE

- As a pre-medication - oral 0.5 mg/kg for children melatonin before surgery and in adults, 5–10 mg of oral melatonin 30–60 min before operation.
- Adjuvant for analgesia after surgery - 3 or 5 mg orally or sublingually

Adverse Effects [52]

Melatonin is typically non-toxic, however some moderate adverse effects with greater dosages and prolonged-release preparations have been documented, including:

a) somnolence

b) Sleepiness in day

c) Headache

d) Sickness

CONTRAINDICATIONS [52]

1. Pregnancy and Breastfeeding: Due to limited safety data, pregnant or nursing women should avoid using melatonin.
2. Renal Dosing: Due to the increased risk of negative consequences from the failure to sufficiently remove melatonin, physicians should be cautious while treating the patient's receiving dialysis.
3. Hepatic Dosing: Physician must used cautiously used when treating individuals whose livers aren't working well because they can't metabolise melatonin as well. Nevertheless, experts came to the conclusion that melatonin did not result in hepatotoxicity based on a number of clinical experiments. Probability grade: E (improbable aetiology of clinically evident liver damage).
4. Auto-immune Disorders: Physicians must use caution when treating individuals who have autoimmune disorders such rheumatoid arthritis or organ transplant rejection. Melatonin promotes the synthesis of interleukins (IL-1,2,6,12) IL-2), IFN- γ, T-helper cells, cytotoxic T-cells, B-cell & T-cell precursors, which in turn boosts the immune system's function. The specific clinical relevance of this phenomenon is still unknown, though.

POTENTIAL CLINICAL APPLICATIONS

Role in Premedication

Melatonin is a desirable substitute for pre-medicating because it has sedation, hypnotic, analgesia, antiinflammatory, antioxidative, & chronobiotic effects [53,54].

The contradictory character of the findings regarding the effectiveness of perioperative melatonin in paediatric patients was supported by a recent systematic review articles [55]. In the acknowledged Samarkandi & peers study [56], melatonin not only reduced preoperative anxiety in children as well as midazolam, but it was also linked to a tendency for a quicker recovery, a lower occurence of anxiety at ten minutes after surgery, & sleep irregularities at postoperative second week than was seen with the midazolam. Contrast, it was found in a different trial that melatonin was more successful than midazolam at declining anxiety in children during anaesthesia induction, delirium emerged less frequently in those who received melatonin than in those who received midazolam [57].

In their study, Nethra S et al. [58] evaluated the impact of oral melatonin taken prior to surgery on postoperative pain & peri-operative nervousness in patients having infra-umbilical surgeries under neuraxial blockade (SAB). 70 ASA 1 & 2 patients between 18 & 60 yrs who had been assigned for infra-umbilical surgery under neuraxial block were randomised into 35 into M & P groups, after receiving acceptance from the hospital ethical committe & obtaining patients' informed consent agreement. One hour before to spinal surgery, all participants administered either 3 mg of peroral melatonin or placebo. Using the Visual Analogue Scale (VAS), post operative ache was evaluated, and the time needed for the initial dose of rescue analgesia was recorded. The HAM-A & RSS were used to measure the levels of perioperative anxiety and sedation, respectively, and to monitor for any negative outcomes. SPSS version 22 was used to examine the data along with the required statistical tests. Both the length of the surgery and the segment of the population were compared in

between the groups. Rescue analgesia needed for noticeably lengthier in the group M (311.839min) then the group-P (189.622.2min) with P valve0.01, & VAS was noticeably lower in M-group throughout the initial six hrs following surgery with P0.01. After taking a melatonin premedication during the perioperative phase, the anxiety levels dramatically lowered with a P-value of 0.01. P- value:0.01, RSScore was greater in the M-group until 2 hours post-surgery. In neither group were there any negative outcomes. The study found that in patients undergoing surgeries under neuraxial block, pre-operative peroral melatonin 3milligram offered analgesic beyond the 1st 6 hours in post operative period, decreased need for analgesia in the 1st 24 hours, and given peri-operative anxiety & sedation instead of any adverse reactions.

Preoperative melatonin might, according to a dose-dependent theory put forth by Lofty M et al. [59], lessen patients' anxiety as well as IO & PO analgesia use. ASSQ scores were considerably less in research groups at 1-hour post-premedication than they were at baseline and at 1 hour in the P-group (participants administered 3 ml of ordinary distil water), & this significance impact persisted for three hours perorally. The reported ASSQ among research groups was 36.9% between groups M1 (3 mg of melatonin) & M2, and 25.9% between groups M2- melatonin & Z- midazolam (melatonin dose:6mg). Preoperative anxiolysis medication reduced PO pain scores, reduced the need for analgesia, and extended the time until the first call for recover analgesia. This benefits were more evident with 6mg of melatonin than with placebo, 3mg melatonin, or midazolam. Pre-operative melatonin, according to the study, is an effective strategy for reducing preoperative anxiety. It also reduced postoperative anxiety, pain scores, and analgesic usage, which facilitated an early recuperation & short postoperative hospital-stay. The preoperative melatonin 6-mg dose was effective and showed no sign of dose dependency.

When administered 120 minutes before to the surgery, melatonin, according to Gupta P et al. [60], can help maintain stable hemodynamic while intubating and doing laryngoscopy & intubation. 60 physical status of ASA Patients in grades 1 & 2, regardless of gender, between 20-45 yrs, in between 40-65 kgs, and planned for elective operations under GA were divided equally into 2 groups: Group C- control & Group M-melatonin. 120 minutes prior to surgery, they were given peroral placebo or 6 mg tab.melatonin . A substantial rise of HR & BP was seen in control group at time of direct laryngoscopy & tracheal intubation, & this increase remained for ten mins following intubation. At the time of direct laryngoscopy & intubation, there was a negligible elevation of HR in the melatonin group; however, this increase quickly subsided after intubation. According to the study's findings, melatonin is a useful medication for reducing the cardiovascular reactions after laryngoscopy and endotracheal intubation.

In two groups of patients having general anaesthesia, Shnayien TA et al. [61] sought to investigate changes in blood pressure and heart rate during endotracheal intubation (melatonin versus control). Patients and Procedures Two equal groups of 60 patients each were randomly allocated (n = 30). Two placebo tablets were given to Group C (the control group) 120 minutes before to surgery. Oral melatonin tablets containing 6 mg (two tablets containing 3 mg each) were given to Group M (the melatonin group) 120 minutes before to surgery. Regarding HR,SBP,DBP showed lower significance in the research group than in the control group prior & after anaesthesia induction, as well as at the moment of tracheal intubation & 5 and 10 mins post intubation ($P<0.001$), even though there was no statistical difference with baseline reading ($P > 0.05$).

Whether pre-anesthetic peroral melatonin mitigates pressor responses to intubation and anaesthetic requirement for the subject of research by Kumar R et al. [62]. The melatonin group or placebo group (sample size = 32 each) was randomly assigned to 64 participants

planned for cholecystectomy laparoscopy. Two pills of melatonin (3 mg each) were given to the melatonin group, while two tablets of vitamin D3 were given to the placebo group 120 minutes before to induction. For 15 minutes both during the induction and after the intubation, hemodynamic parameters were monitored. Additionally noticed were the negative effects of melatonin, the total intraoperative fentanyl use, & the total propofol induction dose. Heart rate (HR) increased more after intubation in placebo group (10.75% versus. 37.08% at 1st min), but less so in the melatonin group (p 0.0001). At one minute after intubation, the melatonin group experienced a lower highest proportion increment in SBP, DBP, & MAP than the placebo group (SBP-9.25% versus. 37.73%, DBP-10.58% versus. 35.51%, and MAP-9.99% versus. 36.45%, respectively) (p 0.0001). The number of patients who further require intra-operative fentanyl (3 versus. 11) and propofol induction dose (1.4 mg/kg versus. 2.0 mg/kg) were both considerably declined in melatonin group.

In order to evaluate the effective nature of melatonin vs a placebo in declining hemodynamic reactions during laryngoscopy and endotracheal intubation, Devi A et al. Additionally, it wants to know if melatonin aids in stabilising intraoperative hemodynamics and reducing extubation reaction. There were 60 patients in the research. Two groups were created out of them. 120 minutes before to surgery, Group M received a 6 mg melatonin tablet, and Group C received a placebo (Vitamin D3). Melatonin group had a substantially less rise in heart rate during laryngoscopy and intubation contrast to control group. (P-0.0029). The change in HR between groups of melatonin & placebo was also noticeably reduced during and after extubation. Following induction, while doing laryngoscopy & endotracheal intubation,& throughout the post intubation duration for the first 10 mins, intraoperatively, the melatonin group's SBP was low. While comparing placebo group, the melatonin group's SBP significantly decreased both during and after extubation. During laryngoscopy, intubation, and at 1st min, 5th min, & 10 mins following intubation,

intraoperatively, during and after extubation, the melatonin group's diastolic blood pressure was lower than that of the placebo group. In the melatonin group, MAP was likewise noticeably lower during the intraoperative period. There was a very significant statistical difference among the two groups both during and post-extubation.

Devtara A et al[64] .'s goal was to evaluate how two different oral melatonin dosages affected the hemodynamic parameters. Subjects and Approaches Ninety patients, 20-45 yrs old, of either gender, with ASA grades 1 & 2, were assigned into three groups at random. Patients posted for elective procedures under GA were the subjects of this randomised prospective study. 120 mins prior to operation, oral placebo was given to Group-C, melatonin 6 mg was administered to Group-M6, and melatonin 9 mg was given to Group-M9. At various time intervals, patients were evaluated for intraoperative and postoperative hemodynamic parameters. The mean heart rate considerably dropped in Groups M6 and M9 from baseline (83.63 6.7) to (81.96 6.1) and from baseline (82.82.09) to (77.4 5.25) respectively (P 0.001), but it increased in Group C from baseline (81.2 5.33) to (92.0 4.64). Systolic blood pressure (SBP) increased in Group C from baseline (123.563.25) to (132.763.77), whereas it significantly dropped in Groups M6 and M9 from baseline (121.133.82) to baseline (118.1331.3) and from baseline (122.793.33) to baseline (115.963.44), respectively. ($P<0.001$) The study found that oral melatonin at dosage of 6 and 9 mg was more beneficial than a placebo, but that 9 mg of melatonin was more effective than 6 mg at mitigating the hemodynamic response to direct laryngoscopy & tracheal intubation.

Melatonin's ability to lessen the haemodynamic alterations that occur during laryngoscopy and intubation was examined by Gandhi M et al. [65]. A total of 100 patients between the ages of 18 and 60 who were ASA grades 1 and 2 were randomised and 100 patients equally split into groups M and C: Group-M received peroral melatonin 6mg, and Group-C received multivitamin tablets with a drop of water nighty mins prior to anaesthesia

induction. At baseline, the mean pulse rates of the two groups were comparable. Both groups' heart rates increased during intubation, significant in the control group and remained for up to 10 minutes, whereas in the melatonin group it began to decrease after 3 minutes. In comparison to the melatonin group, there was a substantial increase in Systolic, Diastolic, and Mean BP in the control group while intubating and post intubation for 5 mins.

Mohamed AK et al[66] .'s goal compared the effects of peroral pregabalin and melatonin on anxiety pre-operatively as well as how well they did at reducing the hemodynamic reactions to endotracheal intubation. Patients and procedures Three equal groups of patients assigned randomly to each group. The control group-C) received 150 mg of pregabalin orally, group (M) received 6 mg of melatonin orally, and group (P) received vit D orally as a placebo two hours before to surgery. All three groups used the same anaesthetic method. Group M and group P had the lowest hemodynamic response to endotracheal reaction and anxiety, respectively, while group C had the greatest levels. In a related study, Chandra DK et al. [67] reported that melatonin and pregabalin showed statistical significant differences (P-value 0.01) in HR, SBP, and RPP from 1 minute after intubation to 8 minutes, as well as MAP at 6 and 8 minutes after intubation. A statistically significant difference among Melatonin group and Pregabalin group and the placebo group was seen in the SBP, DBP, MAP, RPP, and HR at intubation at all subsequent time points. Pregabalin and melatonin groups considerably outperformed the placebo group in terms of sedation scores. With either medicine, no notable side effects were observed. The study found that while pregabalin and melatonin both reduced intubation response, melatonin did so more effectively.

A research by Naguib M et al. [68] compared the perioperative effects of various dosages of midazolam and melatonin. 84 ASA I women participated in the prospective, randomised, double blind, placebo controlled research. Participants were allocated at random

to one of the seven groups and given either sublingual midaz (0.05 mg/kg, 0.1 mg/kg, or 0.2 mg/kg), sub-lingual melatonin (0.05 mg/kg, 0.1 mg/kg, or 0.2 mg/kg) or sublingual saline as a placebo. Prior to premedication, 10, 30, 60, and 90 minutes afterward, as well as 15th, 30th, 60^{th} , & 90 mins following admittance to the PACU room, sedation, anxiety, & orientation were noted. The psychomotor functioning of the patients was evaluated using the DSS test and the TD test. They came to the conclusion that 0.05 mg/kg melatonin as premedication produced effective preoperative sedation & anxiolysis without degrading mental and psychomotor abilities or delaying recovery and also stated as a sufficient dose as premedication.

Assessed peroral melatonin and peroral midazolam effects on anxiousness, cognition, and psycho-motor functioning, preoperatively Patel T et al. [69] studied 120 patients in a randomised fashion. A total of 40 patients from every group of melatonin, midaz, & placebo, ranging in age from 16 to 55 and having been posted for elective surgery by ASA Status 1 and 2, had the procedure. 60-90 minutes prior to induction, patients received a choice of peroral melatonin: 0.4 mg/kg of, of peroral midazolam: 0.2 mg/kg, or a placebo. Using the anxiety, orientation, and sedation scores on the VAS, preoperative anxiety was examined before and 60–90 min after medication administration. Using the DSST and TMT, psychomotor and cognitive skills were examined. When comparing midazolam and melatonin, the VAS anxiety scores did not differ significantly (P-value-0.49). Melatonin (P-value = 0.0258) and midazolam (P-value = 0.0000) showed statistical significance compared to placebo in the inter-group comparison of scores in sedation. They came to the conclusion that peroral melatonin:0.4 mg/kg, offers adequate anxiolysis on par with oral midaz. Peroral melatonin 0.4 mg/kg, unlike midazolam, has no adverse effects on general mental and psychomotor functioning, especially when it comes to cognitive abilities like working memory, recall memory, persisted attention, and though flexibility.

In a research of Khare A et al. [70] on adult participants having various surgical procedures under general anaesthesia, the effects of peroral melatonin and peroral alprazolam as pre-medication were compared. A prospective, randomised, placebo-controlled research was conducted. Ninety carers were participated in this trial, and they were segregated into 3 groups at random. Oral melatonin 6 mg was given to Group M, oral alprazolam 0.5 mg to Group A, and a multivitamin pill was given as a placebo to Group P. Pre-induction medication was given 120 minutes prior to induction. They contrasted sedation, anxiety, cognition, and orientation. According to their study, group M and group A experienced much lower anxiety scores than group P. Alprazolam produced greater sedation than the melatonin and placebo groups. Prior and post pre-medication, orientation doesn't show statistically significance in any of the three groups. Melatonin had a higher cognitive score than alprazolam or a placebo.

ORAL MELATONIN VS CLONIDINE

The goal of Choudhary S et al. study [71] was to assess how peroral melatonin and peroral clonidine affected the pressor reactions to direct laryngoscopy and intubation. Sixty ASA grade 1 and 2 patients, 20-60 yrs old, of either sex, planned to have elective surgeries under GA were randomly allocated to Group M or Group C and given oral doses of melatonin:6mg and 200 mcg of clonidine, respectively, 2 hours prior to anaesthesia induction in this prospective randomised double blind study. The study drug was administered before and 120 min after the haemodynamic measurements of HR, systolic, diastolic, mean blood pressure, and RPP were taken. They were also taken prior to induction, immediate post-intubation, and at 1st, 3rd, and 5th min after intubation. The RSS was used to measure sedation. Among the groups, there was a statistical substantial difference in HR and RPP at 0, 1, 3, and 5 minutes after intubation. At all time points, the RSS varied between 2nd and 3rd. The study found

that, despite the effectiveness of both medications, oral melatonin outperformed peroral clonidine in reducing the pressor reaction to direct laryngoscopy and intubation with nill side effects.

Before inducing general anaesthesia, Banarjee SG et al. [72] studied a comparison between oral Clonidine and Melatonin treatment may reduce reflex hypertension and tachycardia. 76 patients scheduled for general anaesthesia for gastrointestinal procedures were split to 2 groups. Group 1 administered 6mg of oral Melatonin before to surgery, whereas group 2 received oral Clonidine 100 mcg prior to surgery. The Chi square test and unpaired t test, where appropriate, used to compile, tabulate, and statistically evaluate the observation results. In terms of decreasing systolic, diastolic, MAP, & heart rate fluctuations related to direct laryngoscopy & intubation, oral melatonin was found to be superior to oral clonidine. The occurrence of modest pre- and postoperative complications in both groups. In Gastrointestinal surgeries oral Melatonin is effective than oral clonidine under GA.

Kumar R et al[73] .'s goal was to examine how Melatonin and Dexmedetomidine affected a candidate supporting voluntary operation's cardiovascular reactions to laryngoscopy and endotracheal intubation. A minimum of 150 patients were chosen for the study, which was a randomised prospective double-blinded study carried out in Anesthesia & Critical-Care Dept. ASA 1 & 2 patients in between 20-50 yrs, of either gender, who underwent elective middle ear surgery and required general anaesthesia for a procedure lasting longer than 30 minutes, patients with normal airways with Mallampatti grade 1 and 2 , >90 degree neck movement, and no crook teeth, were included in this study after receiving ethical committee approval. DM, HTN, mental illness, sedative usage, anticonvulsants, sleep difficulties, obesity, and drug allergies were among the exclusion criteria. Dexmedetomidine (1g/kg) and melatonin (6 mg each) can both lessen the hemodynamic alterations that occur during laryngoscopy and intubation. There were higher instances of hypotension and

bradycardia in Dexmedetomidine big dose (1g/kg) than in Dexmedetomidine (0.5g/kg). The haemodynamic alterations during laryngoscopy and intubation can be lessened by combining melatonin (6 mg) and low dose dexmedetomidine (0.5 g/kg) than by using just melatonin (6 mg) and dexmedetomidine (1 g/kg) alone.

MATERIAL AND METHODS

Area of Research

Anaesthesia Department in R. L. Jalappa Hospital & Research Hospital center, Kolar

Study Population

Patients who posted for surgeries electively under general anesthesia and fulfilling eligibility standards.

Study Design

A prospective randomized clinical trial was conducted.

The Sample Size Calculation

Formulae :

$$n = \frac{(\kappa * \sigma_1^2 + \sigma_2^2\ [z_{1-\dot{\alpha}/2} + z_{1-\beta}]^2}{\Delta^2}$$

- n = Group sample size
- σ_1= S.D in group-A
- σ_2 = S.D in group-B
- Δ = groups mean difference
- κ = ratio =n_2/n_1
- $z_{1-\dot{\alpha}/2}$ = two sided Z-value ; e.g. Z= 1.96 for 95% C.I Significance level
- $z_{1-\beta}$ = Power

Based on a research study by Choudhary et al with a C.I of 95% and power of 80%. Each group's anticipated sample size was 40.

Study Duration

January 2021 to June 2022.

Inclusion Criteria

1. Age: 20 to 60 years of both gender
2. ASA status: 1 & 2.
3. Informed consent given by patients

Exclusion Criteria

1. Melatonin or clonidine-treated patients
2. Mental disorders
3. Pregnancy
4. Cardiac disorders
5. Renal or Liver Disorders
6. Morbid obese
7. Bleeding diathesis
8. Known allergic reaction to melatonin or clonidine
9. Modified Mallampati class 3 and 4: Predicted difficult airway
10. Patients requiring intubation procedure that took more than 15 seconds or more than two attempts were not included in the analysis.

Methodology

- Following permission from the Ethical Committee of the Institution, the research was conducted.
- Patients gave their assent after being fully informed of the risks and benefits.

- A complete patient history was obtained.
- A complete physical examination was done.
- Routine investigations were conducted.
- An I.V line was secured and IV fluids were given.
  - Using random integers produced by a computer, participants were randomly allocated into two groups.
  - Group M: administered 6 mg melatonin, preoperatively 120 min prior to anaesthetic induction.
  - Group C: Receiving 200 mcg of clonidine, preoperatively 120 min prior to anaesthetic induction.
- Before receiving the study medication, the subjects' HR,SBP,DBP,MAP, and RPP were recorded.
- In the operating theatre, standard monitoring (HR, NIBP, Oxygen saturation, electrocardiogram) was performed, and documented. 18 G IV line secured and infusion of Lactated Ringer's initiated at the flow of 2 ml/kg/hr. Following three minutes of 100% preoxygenation, all patients received intravenous (IV) glycopyrrolate 0.004 mg/kg and intravenous (IV) fentanyl 2 mcg/kg. To assist endotracheal intubation, patients were induced with intravenous (IV) propofol 2 mg/kg, followed by intravenous (IV) vecuronium 0.1 mg/kg. From the moment the laryngoscope blade was inserted until the time the endotracheal cuff was inflated, the total direct laryngoscopy time was recorded.
- Heart rate (HR), systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial pressure(MAP), and rate-pressure product(RPP) were all measured immediately after intubation, as well as 1, 3, 5, and 10 minutes later.

Outcome Variables

- Heart rate
- Systolic blood pressure
- Diastolic blood pressure
- Mean arterial pressure =SBP+2(DBP)÷2
- Rate-pressure product (RPP)= HR × SBP at Baseline

Statistical Analysis

All of the information was recorded in a pre-planned research proforma. Frequency and percentage were used to express qualitative data. The Chi-Square test was used to investigate the relationship between qualitative variables. Mean ± SD was used to express quantitative data. The unpaired t-test used to compare quantitative data among the two groups if the 'Normality test' was passed, and the Mann-Whitney test was used if the 'Normality test' was failed. The significance level was set at < 0.05 p-value. Wherever possible, the results were visually depicted. The majority of the analysis was performed using SPSS Version 26.0, and the graphical representation was created using Microsoft Excel 2021.

RESULTS

Table 1. Distribution of cases as per study drug

Group	Frequency	Percent
Clonidine	40	50
Melatonin	40	50
Sample	80	100

The current study includes 80 patients undergoing elective surgery under general anesthesia. These cases were segregated into two groups of 40 each, randomly which was generated by computer. Group A: Administered 6 mg of melatonin, preoperatively 120 min prior to anesthesia induction and; Group B: Received 200 mcg of clonidine, preoperatively 120 mins prior to anesthetic induction.

Table 2. Gender comparison among study groups

Gender		Group		
		Clonidine	Melatonin	Total
Female	N	25	20	45
	%	62.5%	50.0%	56.3%
Male	N	15	20	35
	%	37.5%	50.0%	43.8%
Total	N	40	40	80
	%	100.00%	100.00%	100.0%
p-value - 0.367				

Present study has 56.3% females and 43.8% males, with comparable gender distribution in the study groups (p-0.367).

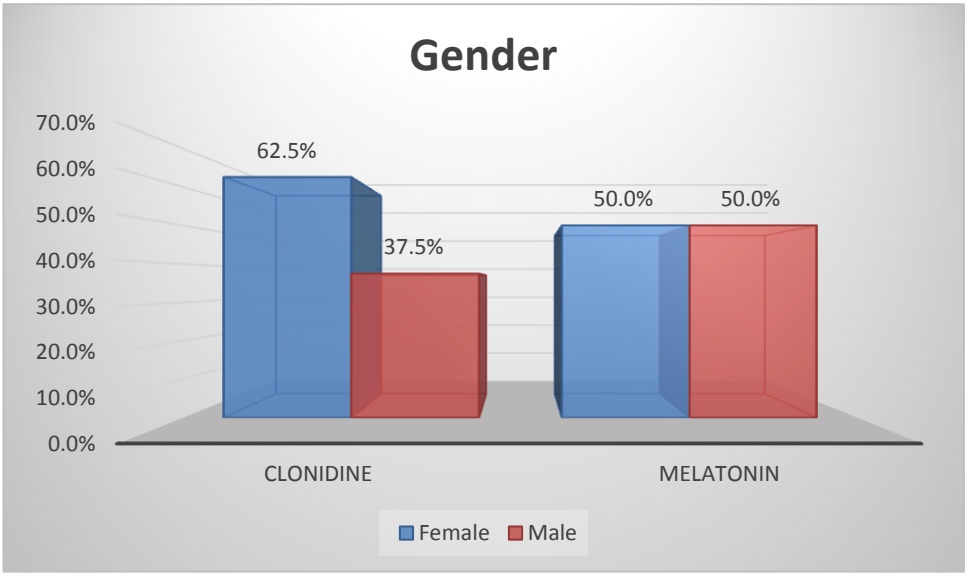

Figure 8: Gender comparison among study groups

Table 3. ASA grade comparison among study groups

ASA Grade		Group		
		Clonidine	Melatonin	Total
I	N	29	32	61
	%	72.5%	80.0%	76.3%
II	N	11	8	19
	%	27.5%	20.0%	23.8%
Total	N	40	40	80
	%	100.00%	100.00%	100.0%
p-value - 0.60				

A total cases of 76.3% were in ASA grade I while 23.8% were in ASA grade II, study groups didn't show statistical distinction (p - 0.60).

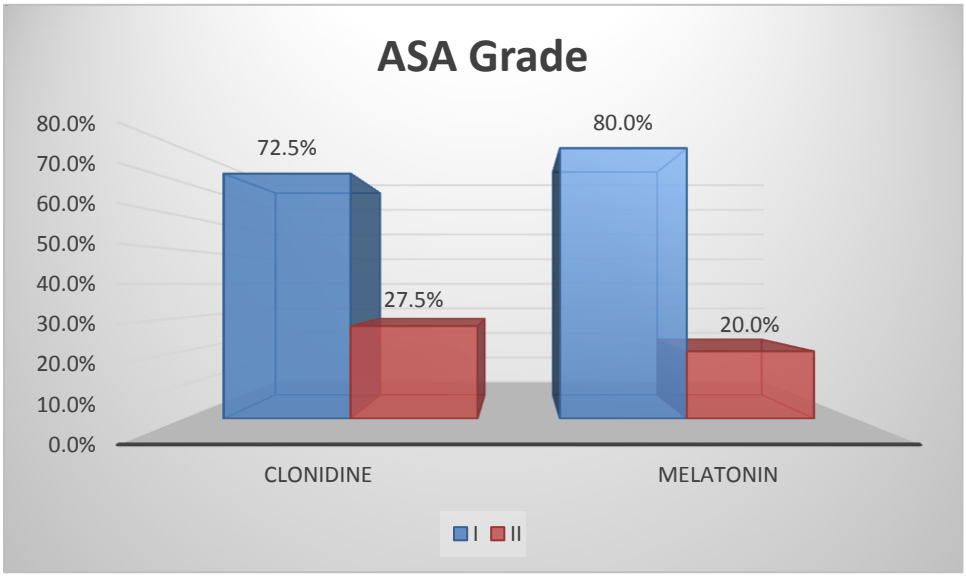

Figure 9: ASA grade comparison among study groups

Table 4. Age and weight mean comparisons between research groups

Variables	Group	N	Mean	SD	p-value
Age (years)	**Clonidine**	40	27.8	4.8	**0.09**
	Melatonin	40	30.9	5.6	
Weight (Kg)	**Clonidine**	40	61.8	9.0	**0.84**
	Melatonin	40	61.3	11.0	

Mean age and weight of the study group was 29.35 years and 61.6 Kg with no difference between study groups (p-0.09 & p-0.84).

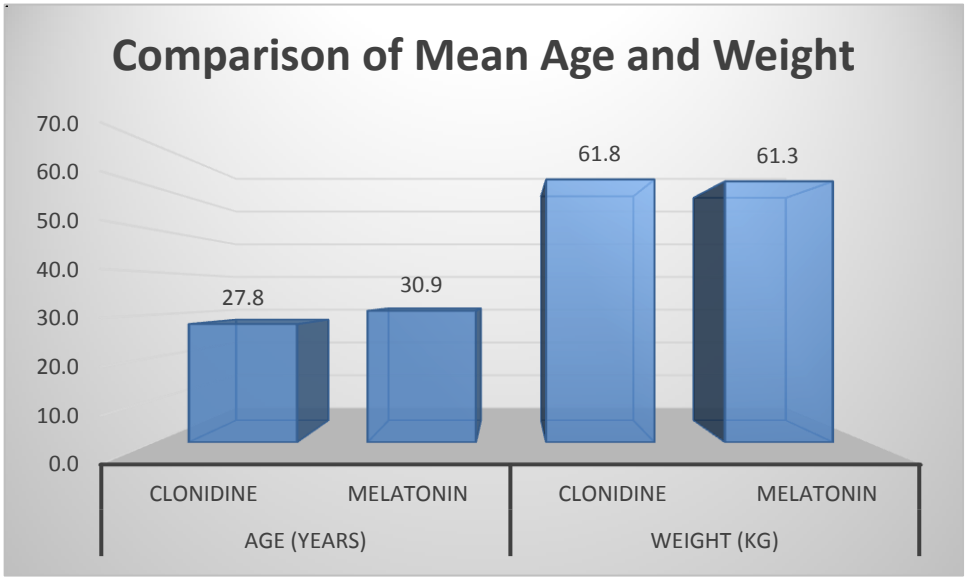

Fig 10: **Comparison of Mean Age and Weight**

Table 5. Mean comparison of study groups as per heart rate

Heart Rate	Group	N	Mean	SD	p-value
Baseline	**Clonidine**	40	78.1	9.3	**0.50**
	Melatonin	40	75.7	17.3	
After Induction	**Clonidine**	40	72.0	8.6	**<0.01**
	Melatonin	40	60.9	15.5	
At 1st min post Intubation	**Clonidine**	40	82.7	6.2	**0.01**
	Melatonin	40	75.5	13.6	
3rd min	**Clonidine**	40	78.9	5.9	**0.01**
	Melatonin	40	72.6	11.1	
5th min	**Clonidine**	40	74.7	5.9	**0.04**
	Melatonin	40	70.2	12.3	
10th min	**Clonidine**	40	75.5	7.9	**<0.01**
	Melatonin	40	68.5	11.6	

In terms of heart rate at baseline, both groups were comparable (78.1 vs 75.7 mins; p-0.50). With baseline heart rate compared the Both groups' heart rates which decreased after induction (p-value<0.01). However, the decline was higher in the melatonin group than in the clonidine group (p<0.01). Following intubation, both groups' heart rates rose, but the elevation was lower than baseline value in melatonin group while it was substantially higher in clonidine group (p-0.01). Post-intubation up until 10 mins, the melatonin group had a considerably reduced mean heart rate. (p<0.01).

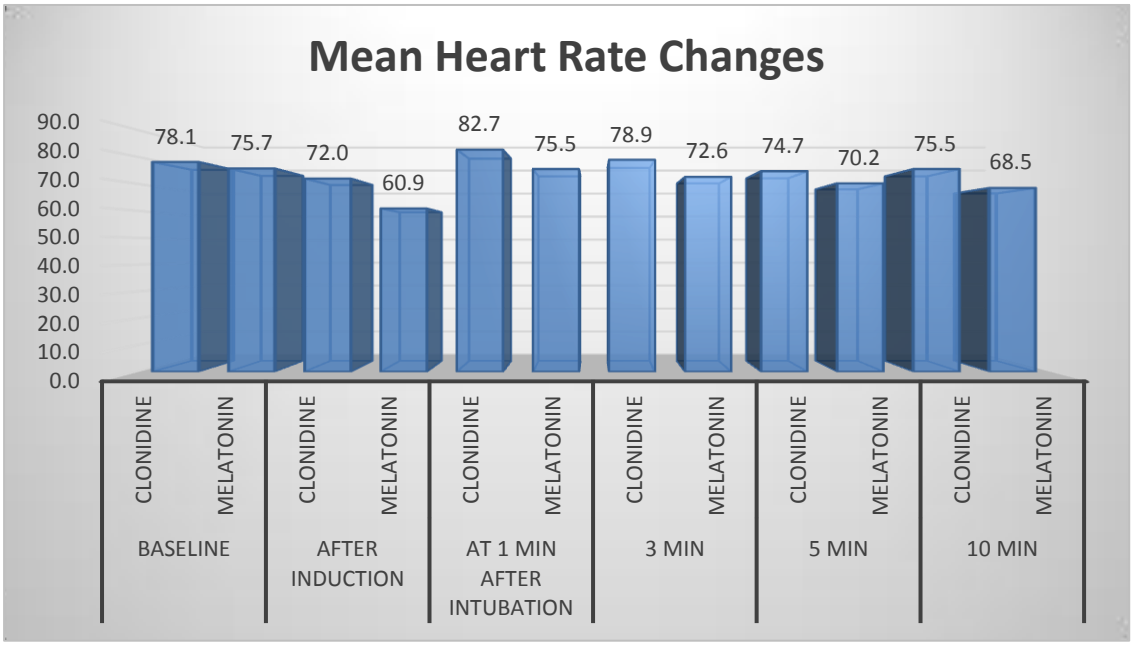

Fig:11: **Mean Heart Rate Changes**

Table 6. Mean comparison of study groups as per systolic blood pressure

SBP	Group	N	Mean	SD	p-value
Baseline	**Clonidine**	40	117.8	6.3	**0.42**
	Melatonin	40	119.7	13.3	
After Induction	**Clonidine**	40	107.5	7.2	**0.37**
	Melatonin	40	109.7	14.3	
At 1st min post Intubation	**Clonidine**	40	117.0	6.8	**<0.01**
	Melatonin	40	110.7	8.3	
3rd min	**Clonidine**	40	111.8	8.0	**0.01**
	Melatonin	40	106.5	8.2	
5th min	**Clonidine**	40	112.5	7.4	**<0.01**
	Melatonin	40	103.6	6.7	
10th min	**Clonidine**	40	110.0	7.6	**<0.01**
	Melatonin	40	99.2	8.9	

Allocated groups were compared with regards to SBP at baseline (117.8 versus 119.7 mm Hg; p-value 0.42). Post induction, compared to baseline, the Systolic BP fell in two groups(p-value<0.01). The SBP increased in two groups post-intubation, but the rise was evidently lower in the group of melatonin as compared to clonidine group (p-value<0.01). Following intubation until 10 mins, the mean SBP was substantially less in the group of melatonin (p<0.01).

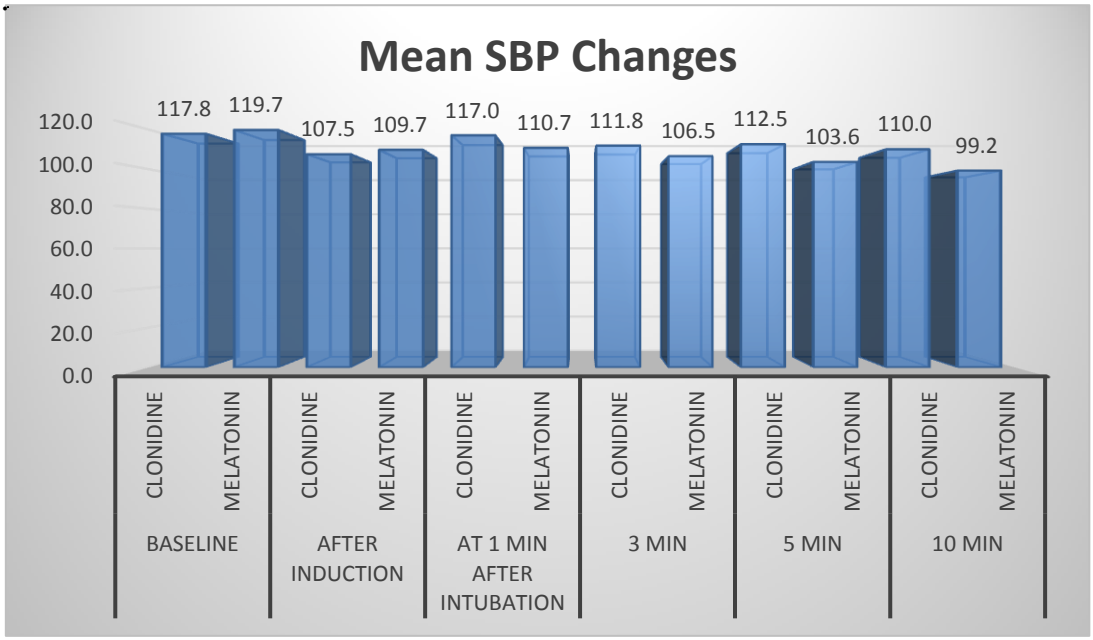

Fig:12: **Mean SBP Changes**

Table 7. Mean comparison of study groups as per diastolic blood pressure

DBP	Group	N	Mean	SD	p-value
Baseline	**Clonidine**	40	69.6	4.8	**0.73**
	Melatonin	40	68.9	9.9	
After Induction	**Clonidine**	40	64.0	3.3	**0.44**
	Melatonin	40	65.6	12.8	
At 1st min post Intubation	**Clonidine**	40	74.2	5.8	**<0.01**
	Melatonin	40	70.2	6.0	
3rd min	**Clonidine**	40	69.6	5.2	**0.018**
	Melatonin	40	64.9	10.9	
5th min	**Clonidine**	40	68.0	5.2	**<0.01**
	Melatonin	40	61.8	9.6	
10th min	**Clonidine**	40	65.1	7.3	**<0.01**
	Melatonin	40	58.4	10.5	

Both groups compared in terms of SBP at baseline (69.6 vs 68.9 mm Hg; p-0.73). Post induction, with baseline comparison, the DBP declined in two groups (p-value<0.01). The DBP increased in two groups post-intubation, but the rise was markedly lower in melatonin group as compared to clonidine group (p-value<0.01). Following intubation until 10 mins, the melatonin group showed lower mean DBP (p-value<0.01).

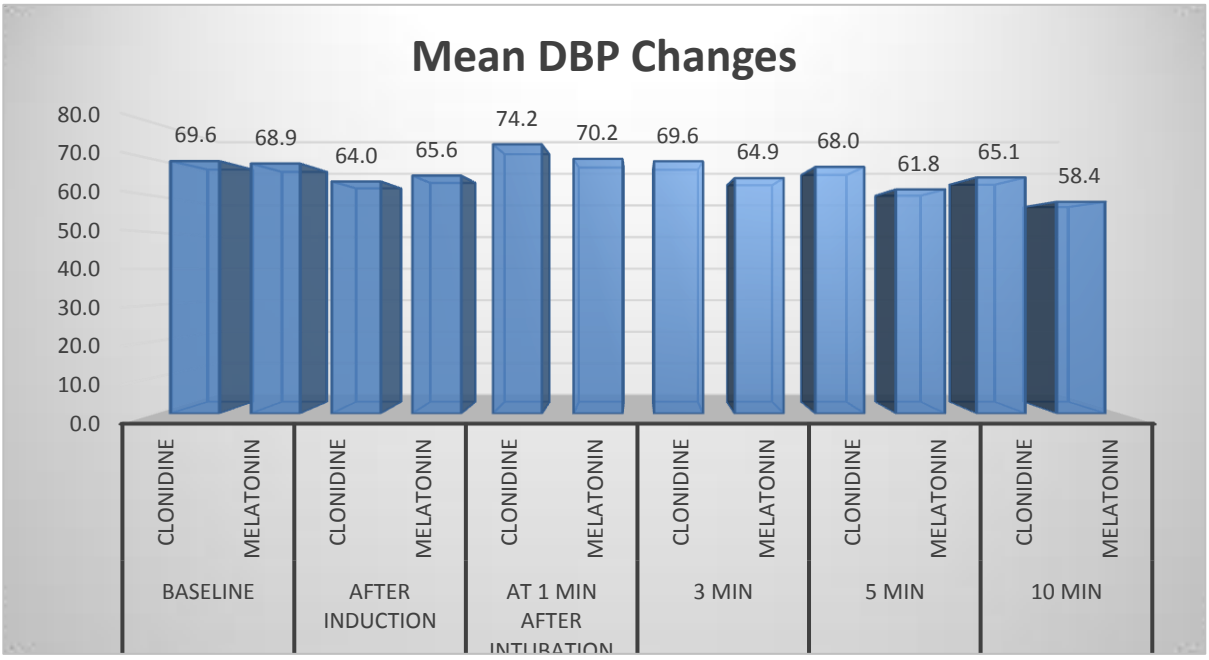

Fig 13: Mean DBP Changes

Table 8. Comparison of study groups as per mean arterial pressure

MAP	Group	N	Mean	SD	p-value
Baseline	**Clonidine**	40	84.0	4.9	**0.22**
	Melatonin	40	86.3	10.2	
After Induction	**Clonidine**	40	78.8	3.6	**0.53**
	Melatonin	40	80.1	12.6	
At 1st min post-Intubation	**Clonidine**	40	88.3	4.5	**<0.01**
	Melatonin	40	83.6	5.5	
3rd min	**Clonidine**	40	83.6	5.5	**<0.01**
	Melatonin	40	78.5	7.4	
5th min	**Clonidine**	40	82.8	4.6	**<0.01**
	Melatonin	40	75.6	7.8	
10th min	**Clonidine**	40	80.3	6.8	**<0.01**
	Melatonin	40	71.9	9.8	

The two groups were compared in terms of mean arterial pressure (MAP) at baseline (84 vs 86.3 mm Hg; p-0.22). Post induction, the MAP declined in two groups when compared to baseline (p- value: <0.01). The MAP increased in allocated groups post-intubation, but the rise was noticeably lower in group of melatonin when compared to clonidine group (p<0.01). Post-intubation till 10 minutes, the MAP was substantially reduced in melatonin group (p-value:<0.01).

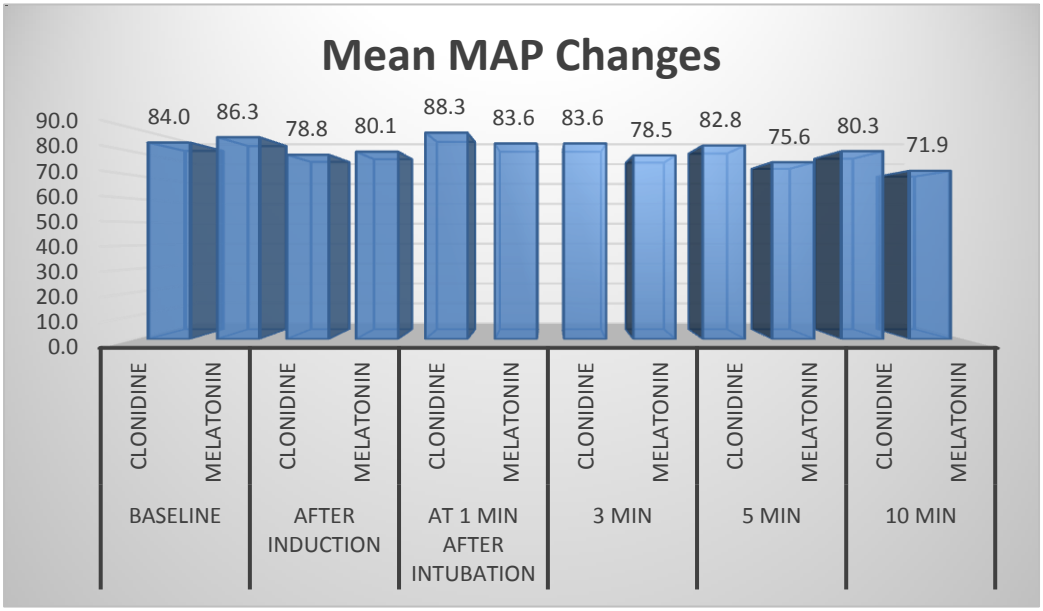

Fig 14: Mean MAP Changes

Table 9. Mean comparison of study groups as per Rate Pressure Product

RPP	Group	N	Mean	SD	p-value
Baseline	**Clonidine**	40	9203.7	1437.6	**0.69**
	Melatonin	40	9061.3	2263.4	
After Induction	**Clonidine**	40	7733.2	1056.0	**<0.01**
	Melatonin	40	6675.2	1492.4	
At 1st min post Intubation	**Clonidine**	40	9673.6	925.5	**<0.01**
	Melatonin	40	8309.4	1353.8	
3rd min	**Clonidine**	40	8812.3	855.2	**<0.01**
	Melatonin	40	7721.7	1285.7	
5th min	**Clonidine**	40	8400.6	874.0	**<0.01**
	Melatonin	40	7277.0	1409.2	
10th min	**Clonidine**	40	8303.1	1102.0	**<0.01**
	Melatonin	40	6788.2	1300.0	

The designated groups were compared in terms of mean RPP vale at baseline (9203.7 vs 9061.3 mm Hg; p-0.73). Post induction, the RPP declined in two groups when compared to baseline (p-value: <0.01). Post-intubation, RPP rise in two groups, but the rise was evidently more in clonidine group (p<0.01). Following intubation until 10 mins, the mean RPP was substantially more in clonidine group (p<0.01).

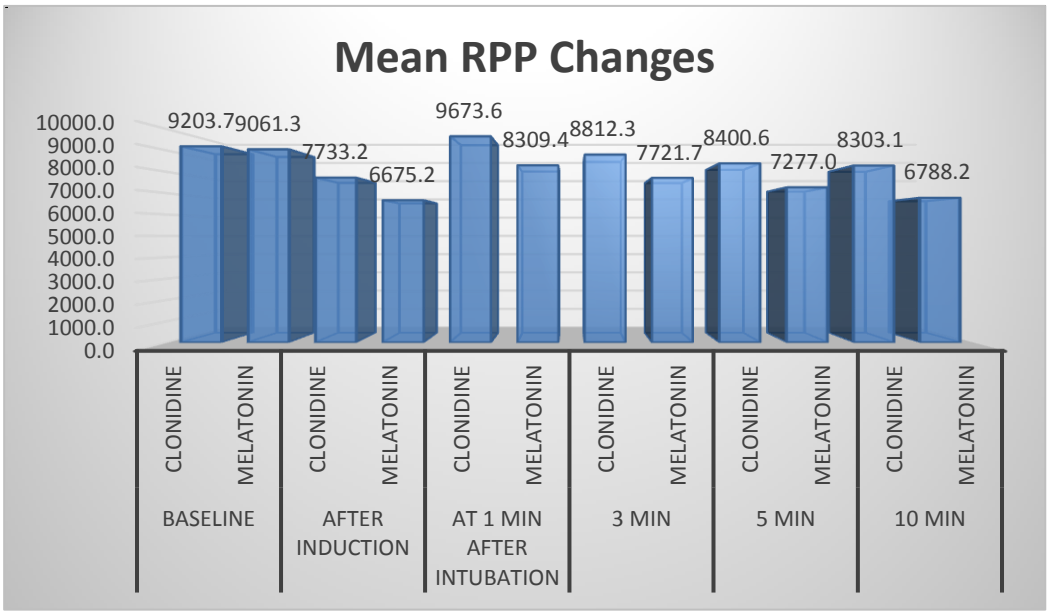

Fig 15: **Mean RPP Changes**

Table 10. Mean evaluation of study groups as per complications

ADRs		Group		
		Clonidine	Melatonin	Total
Hypotension	N	0	0	0
	%	0.0%	0.0%	0.0%
Bradycardia	N	0	0	0
	%	0.0%	0.0%	0.0%
PONV	N	0	0	0
	%	0.0%	0.0%	0.0%

None of the groups showed any complications like hypotension, bradycardia and PONV during the procedure or post-operatively.

DISCUSSION

The hemodynamic response to direct laryngoscopy and endotracheal intubation elicits sympathetic reflex triggered by epipharyngeal and laryngeal stimulation resulting in significant rise in heart rate and blood pressure. [1].

The epipharyngeal region elicited the greatest reflex hypertensive response, while the tracheobronchial tree contributed the least. Stimulation of all the sites of the respiratory tract enhanced the frequency of discharge of the efferent cervical sympathetic fibers. They were statistically significant for stimulation of the epipharynx and larynx. [16].

This reflex circulatory response appears to be independent of the anesthetic agents used. The depth of anesthesia obtained is the more important factor. The changes are exaggerated by straining, coughing on the endotracheal tube and Hypercarbia. The response is triggered by the laryngoscopic blade pressing against the tongue base or by elevating the epiglottis, depending on the kind of blade employed. In theory, blind nasal intubation may cause less of pressor response as laryngoscopy is avoided. Laryngoscopy in addition to pressor response could cause arrhythmias [1].

The hemodynamic alterations that cause the increase in blood pressure are challenging to evaluate. The rise in heart rate is likely due to cardioacceleratory activity, which is more pronounced when laryngoscopy is performed alone. Endotracheal intubation activates not only the autonomic nervous system but also the central nervous system, as demonstrated by an increase in electroencephalographic activity and basal metabolic rate. [1].

Pressor response has been associated since the introduction of laryngoscopy and intubation. Various methods have been adopted to reduce these pressor responses. However, each method and drugs have certain drawbacks, such as respiratory depression, hypotension,

rebound hypertension and either increase or decrease heart rate Hence, there is always a look out for a novel method or drug to overcome the pressor response

Clonidine and dexmedetomidine, two α2-adrenoceptor agonists, offer an alternative to commonly used supplementary anaesthetic drugs due to their anaesthetic-sparing and hemodynamic-stabilizing actions [5]. Clonidine is a central sympatholytic α2-adrenoreceptor agonist. Clonidine premedication reduces the haemodynamic stress reactions to direct laryngoscopy and endotracheal intubation. Clonidine also maintains blood pressure by enhancing the sensitivity of the cardiac baroreceptor reflex [6].

Tanaka M et al. [29] in their research observed that peroral clonidine administered 30 to 90 minutes prior to surgery attenuates the hemodynamic responses to intubation, reduces anesthetic doses and also opioid requirements.

Ghignone M et al. [30] also observed that oral clonidine 5μg/kg 90 minutes before induction of anesthesia reduces fentanyl requirements by 45% when compared to routine premedication.

Batra YK et al. [32] and Sukanya M et al. [33] studies suggested that the elevation of heart rate and blood pressure related with direct laryngoscopy and endotracheal intubation during a routine induction process can be mitigated by the use of peroral clonidine.

Chadha R at al. [34] study showed that oral clonidine pretreatment effectively counters haemodynamic instability i.e. tachycardia and hypertension due to laryngoscopy in craniotomy. They also found that sleep dose of thiopental was reduced after pretreatment with clonidine.

Arshi K et al. [40] assessed premedication oral Clonidine for mitigation of haemodynamic response to direct laryngoscopy and intubation. Study revealed anxiety, systolic, diastolic & mean blood pressure and heart rate were all shown to be reduced by

clonidine at 90 minutes. The clonidine group outperformed the placebo group in terms of preventing an rise in systolic blood pressure and heart rate during intubation.

In present study too, clonidine substantially attenuates the hemodynamic stress response of direct laryngoscopy and intubation. Hemodynamic measures i.e., heart rate and blood pressure reduced significantly after induction with drugs. Post-intubation, all the hemodynamic parameters showed transient increase, but all of them returned to the initial value at the end of 3 minutes and remained below baseline values after that.

Melatonin, also known as N-acetyl-5-methoxytryptamine, is a naturally occurring hormone that helps regulate sleep and is released by the pineal gland. Melatonin administered exogenously promotes sleep onset and enhances sleep quality. Unlike benzodiazepines and its analogues, it does not cause cognitive impairment and instead induces a more natural sleep pattern [7]. Adults and children have been premedicated with this medicine in a variety of dosing regimens by a number of studies.

Gupta P et al. [60] research hypothesised that 120 min before laryngoscopy and intubation, administration of melatonin offers hemodynamic stability. The control group experienced a substantial rise in heart rate and blood pressure during laryngoscopy and intubation, which lasted for 10 minutes after intubation. The melatonin group experienced a small rise in heart rate during laryngoscopy and intubation, which resolved after 1 minute of intubation. Study concluded that melatonin is an efficient medication in mitigating stress responses during direct laryngoscopy and endotracheal intubation.

Shnayien TA et al. [61] also observed that there was no statistically significant variation between BP and HR at baseline value ($P > 0.05$); Nevertheless, HR and BP was considerably lower before and after anaesthetic induction, as well during tracheal intubation and 5th and 10th min post intubation in study group compared to control group (P-value < 0.001).

Devi A et al. [58] in another placebo-controlled trial observed significant reduction in blood pressure and heart rate in the group of melatonin during intubation, while extubating and post-extubation period versus placebo.

Gandhi M et al. [60] study also observed that the control group's SBP, DBP and MAP significantly elevated in comparison to the melatonin group during and after intubation for 5 minutes.

In present study too, premedication with oral melatonin significantly mitigates the hemodynamic stress response of direct laryngoscopy and intubation. Hemodynamic variables i.e., heart rate & blood pressure decreased significantly after induction with drugs. Post-intubation, all the hemodynamic parameters showed transient increase, but remained comparable to the the baseline value. The parameters decreased further thereafter and were lower than baseline in all the readings till 10 minutes.

There are very few trials in the literature comparing the efficacy of oral melatonin compared α-2 adrenoreceptor agonist like peroral clonidine & dexmedetomidine in mitigating the hemodynamic response to direct laryngoscopy and endotracheal intubation. Present study was thus planned to fill this lacunae in literature.

Our study included 80 cases posted for surgeries electively under general anesthesia. Participants were segregated into two groups of 40 each, randomly numbers allocated by using computer. Group A: Administered 6 mg of oral melatonin, preoperatively 120 min prior to anesthetic induction and; Group B: Received 200 mcg of clonidine, preoperatively 120 min prior to anesthetic induction.

Mean age and weight of the study group was 29.35 years with 56.3% females and 43.8% males. The two groups were compared with regards to age and gender distribution & baseline hemodynamic variables like heart rate, blood pressure and rate pressure product ($p>0.05$).

Post induction, the heart rate fell in both the groups ($p<0.01$) as compared to baseline. However, the fall was greater in melatonin group in comparison to clonidine group ($p<0.01$). The heart rate elevated in both groups post-intubation, but the increment was lower than baseline value in melatonin group while it was substantially elevated in clonidine group (p-0.01). Post-intubation till 10 minutes, the mean heart rate was significantly lower in melatonin group ($p<0.01$). Similarly, post-intubation, blood pressure increased in the two groups, but the rise was substantially lower in the group of melatonin as compared to clonidine group ($p<0.01$). Post-intubation over 10 minutes, the mean SBP was considerably lower in the melatonin group ($p<0.01$). None of the group experienced any side-effects.

Choudhary S et al. [71] aimed to assess the efficacy of peroral melatonin and clonidine during direct laryngoscopy and intubation in reducing the haemodynamic responses. Heart rate and Rate pressure product were significantly different across groups at 0,1,3, & 5 minutes after intubation. Even though both drugs are efficient, peroral melatonin outperformed oral clonidine in reducing pressor response to direct laryngoscopy and tracheal intubation and none showed adverse reactions.

Banarjee SG et al. [72] did comparative research comparing the effectiveness of oral Clonidine and Melatonin in reducing reflex hypertension and tachycardia prior to induction of general anaesthesia. Systolic, Diastolic, Mean arterial pressure, & heart rate variations related with laryngoscopy and intubation were all shown to be reduced effectively by Melatonin than by Clonidine orally. Perioperative and postoperative problems are common in both groups were comparable and were minor. Gastrointestinal surgeries under general anaesthesia, the current study found that oral Melatonin was more effective than oral Clonidine in haemodynamic stability maintenance.

In one another study, Kumar R et al. [73] sought to determine if Melatonin and Dexmedetomidine might reduce the adverse cardiovascular response to intubation and laryngoscopy. Melatonin (6mg) and dexmedetomidine (1g/kg) were shown to reduce hemodynamic alterations during direct laryngoscopy and intubation in study. Dexmedetomidine (1g/kg) than with a smaller dose (0.5 g/kg) showed more instance of hypotension and bradycardia. Melatonin (6 mg) and Dexmedetomidine (0.5 g/kg) in combination can mitigate hemodynamic alterations during direct laryngoscopy and intubation more effectively than either melatonin (6 mg) or Dexmedetomidine (1 g/kg) alone.

Thus, to summarize, observations made in present study and by the two comparative studies mentioned above, leads us to conclude that mitigation of hemodynamic response to intubation was better by melatonin than clonidine. We thus recommend use of oral melatonin for mitigating the hemodynamic response to intubation and laryngoscopy.

SUMMARY

Comprehensive research was conducted from Department of Anesthesia at Tertiary-care hospital, Tamaka, Kolar. Study aimed to assess the effectiveness of peroral melatonin compared to peroral clonidine in mitigating the pressor response to intubation and laryngoscopy. The current study involved 80 cases of elective surgery under general anesthesia. These cases were sorted into 2 groups of 40 each, randomly generated by using computer: Group-M: Received 6 mg of melatonin, preoperatively 120 mins prior to induction of anesthesia and; Group-C: Received 200 mcg of clonidine, preoperatively 120 mins preceding induction of anesthesia. Following observations were made during the study:

8. Present study has 56.3% females and 43.8% males, with comparable gender distribution in the study groups (p-0.367).
9. A total of 76.3% of the cases were in ASA grade I while 23.8% were in ASA grade II, with no distinction between the study groups (p-0.60).
10. Mean age and weight of the study group was 29.35 years and 61.6 Kg with no difference between study group (p-value 0.09 and p-value 0.84).
11. On basis of heart rate at baseline, both groups were comparable (78.1 vs 75.7 mins; p-0.50). Post induction, the heart rate fell in both groups ($p<0.01$) as compared to baseline. However, the fall was greater in melatonin group as compared to clonidine group ($p<0.01$). The heart rate increased in both groups post-intubation, but the rise was lower than baseline value in melatonin group while it was significantly higher in clonidine group (p-0.01). Post-intubation till 10 minutes, the mean heart rate was significantly lower in melatonin group ($p<0.01$).
12. The assigned groups were comparable with regards to SBP, DBP & MAP at baseline (p-value>0.05). Post induction, compared the two groups in terms of blood pressure reduction, with baseline BP. Post-intubation, blood pressure increased among both

groups, but the increment was substantially lower in the melatonin group as compared to the clonidine group ($p<0.01$). Post-intubation up until 10 minutes, the mean SBP was substantially reduced in melatonin group (p-value<0.01).

13. Both the assigned groups were compared with regards to mean RPP vale at baseline (9203.7 vs 9061.3 mm Hg; p-0.73). Post induction, the RPP declined in both groups as compared to the baseline (p-value:<0.01). Post-intubation, RPP rise in two groups, but the rise was significantly more in the clonidine group ($p<0.01$). Post-intubation up until 10 minutes, the mean RPP was substantially more in the clonidine group (p-value:<0.01).
14. Both groups showed any complications like hypotension, bradycardia and PONV during the procedure or post-operatively.

CONCLUSION

In current study we found a substantial reduction in Heart rate, Systolic, Diastolic, Mean Blood pressures, and Rate Pressure product by both melatonin & clonidine. However, mitigation of hemodynamic response to intubation was better by melatonin than clonidine. This fall in HR and BP is mainly by the centrally mediated sympatholytic effect of the drugs. None of the cases experienced any adverse reactions like hypotension or bradycardia in both groups. We thus recommend use of oral melatonin for mitigating the pressor response to laryngoscopy and intubation.

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ANNEXURE
PROFORMA

Comparative study of oral melatonin and oral clonidine for the attenuation of hemodynamic response to laryngoscopy and tracheal intubation in elective surgeries under general anaesthesia.

Investigators: Dr Sundeep Kalimisetty/ Dr Kiran.N

1.Name of the patient: **2. Age/Sex:** **3. IP No. :**

4.Ward: **5. ASA grade:**

- **General physical examination:**

Height: Weight: Pulse rate: BP:

Pallor/icterus/cyanosis/clubbing/lymphadenopathy/edema

- **Systemic examination:**

RS - **CVS -**

CNS - **P/A -**

- **Investigations :**

Blood group: Hb: WBC: Platelets: RBS:

Blood urea: Sr. Creatinine: Sodium: Potassium: ECG:

PROFORMA (continued)

- **Diagnosis :** **Surgery:**

- **Group M:** Receiving 6 mg of melatonin, preoperatively 120 min before induction of anaesthesia.

- **Group C**: Receiving 0.2 mg of clonidine, preoperatively 120 min before induction of anaesthesia.

Baseline vitals:

HR: SBP : DBP: MAP: RPP:

GROUP :

TIME	HR	SBP	DBP	MAP	RPP
Baseline before giving drug					
Immediately after Intubation					
1 min post-Intubation					
3 min post-Intubation					
5 min post-Intubation					
10 min post-Intubation					

PATIENT INFORMATION SHEET

Study: Comparative study of oral melatonin and oral clonidine for the mitigation of hemodynamic response to laryngoscopy and tracheal intubation in elective surgeries under general anaesthesia.

Investigators: Dr Sundeep Kalimisetty/ Dr Kiran.N
Study location: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.
Details - All patients posted for elective surgery under General anaesthesia.

This study aims to compare oral melatonin and oral clonidine in attenuation of hemodynamic response to laryngoscopy and endotracheal intubation undergoing elective surgery under general anaesthesia.The oral melatonin 6mg or 0.2mg clonidine will be given 2hours before intubation and monitoring of hemodynamic parameters before and after intubation.However, Clonidine and Melatonin may cause sedation and haemodynamic changes but doctors will take care of your well-being.The procedure has been explained in their understandable language orally.

Please read the information and discuss it with your family members. You can ask any questions regarding the study. If you agree to participate in the study, we will collect information. Relevant history will be taken. All information collected from you will be kept confidential and will not be disclosed to any outsider. This information collected will be used only for the dissertation and publication.Your identity will not be revealed. There is no compulsion to take part in this study if you are not convinced. The care and treatment given will not alter irrespective of your participation in this study.There will not be any monetary benefits/Incentives for taking part in this study. You are required to sign/ provide a thumb impression only if you voluntarily agree to participate in this study.

For further information contact
Dr.Sundeep Kalimisetty
Postgraduate
Dept of Anaesthesia, SDUMC Kolar
Mobile no: 8886035500

INFORMED CONSENT FORM

Name of the institution: SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH.

Title of the project: Comparative study of oral melatonin and oral clonidine for the mitigation of hemodynamic response to laryngoscopy and tracheal intubation in elective surgeries under general anaesthesia.

Name of the principal investigator: Dr. Sundeep. K

Name of the guide: Dr. Kiran.N

Name of the subject/participant:

I, _____ aged _____ ,after being explained in my own vernacular language about the purpose of the study and the risks and complications of the procedure, hereby give my valid written informed consent without any force or prejudice for taking oral melatonin or oral clonidine before induction for general anesthesia. The nature and risks involved have been explained to me to my satisfaction. I have been explained in detail about the study being conducted. I have read the patient information sheet and I have had the opportunity to ask any question. Any question that I have asked, have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research. I hereby give consent to provide my history, undergo physical examination, the procedure, investigations and provide its results and documents etc to the doctor / institute etc. All the data may be published or used for any academic purpose. I will not hold the doctors / institute etc responsible for any untoward consequences during the procedure / study. I am aware of there will not be any monetary benefits/Incentives for taking part in this study.A copy of this Informed Consent Form and Patient Information Sheet has been provided to the participant.

Name of Patient: Signature of Patient : _____

Name of Attendant: Signature Patient. Attendant : _____

Relation with patient:

DATE:

Investigator signature:

KEYS TO MASTER CHART

S. No	Serial Number
UHID	Unique Health Identification Number
F	Female
M	Male
HR	Heart Rate
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
RPP	Rate Pressure product
AI	After Induction
AI1	After Induction at 1 minute
AI3	After Induction at 3 minutes
AI5	After Induction at 5 minutes
AI10	After Induction at 10 minutes
PONV	post operative Nausea and Vomiting