AN OBSERVATIONAL STUDY TO COMPARE THE EFFECT OF TWO DIFFERENT DOSES OF DEXMEDETOMIDINE ON HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

By

DR. RIDDHI AGRAWAL

Dissertation Submitted to

Sumandeep Vidyapeeth, Pipariya, Vadodara.

In partial fulfillment

of the requirements for the degree of

M.D.

ANAESTHESIOLOGY

Under the guidance of:

DR. MALINI MEHTA(M.D.)

(PROFESSOR)

DEPARTMENT OF ANAESTHESIOLOGY,

SBKS MEDICAL INSTITUTE & RESEARCH CENTRE,

PIPARIA-391760

2014-2017

Sumandeep Vidyapeeth
Institutional Ethics Committee (SVIEC)

Declerad as deemed to be university u/s 3 of UGC act of 1956
At & Po Pipariya,Ta. Waghodia,
Dist. Vadodara-391760 (Gujarat) India , Phone :+02668-245262/64/66
E-Mail : rd.sumandeep@gmail.com | www.sumandeepuniversity.co.in

Dr. Riddhi Agrawal (Resident)
Department of Anaesthesiology
SBKS MI&RC, DGH,
Sumandeep Vidyapeeth,
Piparia, Waghodia Road,
Vadodara-391760
Gujarat.

Date: 10th Mar 2015

SUMANDEEP VIDYAPEETH
INSTITUTIONAL ETHICS COMMITTEE
OUTWARD: SVIEC/DM/MED/BNPG/141
DATE: 10-3-15
SIGN:
D15006.

Ref: Your study synopsis entitled **"**An Observational study to compare the effect of two different doses of Dexmedetomidine on haemodynamic response to laryngoscopy and endotracheal intubation." Submitted to the SV IEC for approval.

Sub: Approval for conducting the referenced study

Dear Dr. Riddhi,

The Sumandeep Vidyapeeth Institutional Ethics Committee (SV IEC) is in receipt of your above mentioned study document and as the research study classifies in the minimal risk category; as recommended by HRRP SBKS MI&RC. The SV IEC approves your study to be conducted in the presented form.

The approval remains valid for a period of 1 year. In case the study is not initiated within one year, the Ethics Committee expects to be informed about the reason for the same and a fresh approval will have to be obtained subsequently.

The Sumandeep Vidyapeeth Institutional Ethics Committee expects to be informed about the progress of the study (every 6 months), any Serious Adverse Event (SAE) occurring in the course of the study, and if any changes are made in the protocol or patient information/informed consent the SVIEC needs to be informed about this in advance and an additional permission is required to be taken. The SV IEC also requires you to submit a copy of the final study report.

HRRP
S.B.K.S.M.I.R.C.
Outward No. 162
Date 11/3/15
Sign.

Dr. Niraj Pandit
Sumandeep Vidyapeeth
Institutional Ethics committee

SUMMANDEEP VIDYAPEETH
INSTITUTIONAL ETHICS COMMITTEE
AT & P.O. PIPARIA, TAL. WAGHODIYA
DIST. VADODARA-391760.

Sumandeep Vidyapeeth
Institutional Ethics Committee (SVIEC)

Declared as deemed to be university u/s 3 of UGC act of 1956
At & Po Pipariya, Ta. Waghodia
Dist. Vadodara-391760(Gujarat), India, Phone: +2668-245262/64/66
E-mail: rd.sumandeep@gmail.com www.sumandeepuniversity.co.in

SUMANDEEP VIDYAPEETH
INSTITUTIONAL ETHICS COMMITTEE
OUTWARD : SVIEC/Law/Medi/BNPG/15/D16139
DATE : 21-10-16
SIGN. :

Date: 21st Oct 2016

STUDY COMPLETION CERTIFICATE

This is to certify that your study synopsis entitled: "An observational study of compare the effect of two different doses of Dexmedetomidine on haemodynamic response to laryngoscopy and endotracheal intubation." Research Project was done by **"Dr. Riddhi Agrawal"** (3rd year Resident, Dept of Anaesthesiology, S.B.K.S MI & RC, Dhiraj Hospital, Piparia, Waghodiya road, Vadodara-391760, Gujarat) and it was conducted to the satisfaction of the Sumandeep Vidyapeeth Institutional Ethics committee.

Dr. Niraj Pandit
Member Secretary
SV Institutional Ethics committee

SUMANDEEP VIDYAPEETH
INSTITUTIONAL ETHICS COMMITTEE
At. & Po. Piparia. Ta. Waghodia.
Dist. Vadodara-391760.

21/10/2016

Co-ordinator HRRP
S.B.K.S.M.I.R.C.
Sumandeep Vidyapith

HRRP
S.B.K.S.M.I.R.C.
Outward No. 690
Date 21.10.2016
Sign.

SUMANDEEP VIDYAPEETH

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation/thesis entitled**"An Observational study to compare the effect of two different doses of Dexmedetomidine on haemodynamic response to laryngoscopy and endotracheal intubation"** is a bonafide and genuine research work carried out by me under the guidance of **Dr.Malini Mehta, MD ANAESTHESIOLOGY (Professor).**

Date: **Dr.Riddhi Agrawal**
Place: Vadodara

SUMANDEEP VIDYAPEETH

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"An Observational study to compare the effect of two different doses of Dexmedetomidine on haemodynamic response to laryngoscopy and endotracheal intubation"** is a bonafide record of research work done by **Dr.Riddhi Agrawal** in partial fulfillment of the requirement for the degree of MD Anaesthesiology, under my supervision and guidance.It is certified that the study is original.

Date:
Place: Vadodara

Dr.Malini Mehta
MD Anaesthesiology
Professor
Department of Anaesthesiology

SUMANDEEP VIDYAPEETH

ENDORSEMENT BY

HEAD OF THE DEPARTMENT & DEAN

This is to certify that the dissertation entitled **"An Observational study to compare the effect of two different doses of Dexmedetomidine on haemodynamic response to laryngoscopy and endotracheal intubation"** is a bonafide research work done by **Dr.Riddhi Agrawal** under the guidance of **Dr.Malini Mehta, MD (Prof.), Department of Anaesthesiology, SBKS Medical College & Dhiraj Hospital, Piparia, Vadodara.**

Dr.Hetal Parikh
(Prof. and HOD)
Dept. of Anaesthesiology

Date:
Place: Vadodara

Dr. G. V. Shah
(Dean of SBKS Medical Institute & Research Centre)

Date:
Place: Vadodara

SUMANDEEP VIDYAPEETH

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that Sumandeep Vidyapeeth has the rights to preserve, use and disseminate this dissertation / thesis in print or electronic format for academic / research purpose.

Date: **Dr. Riddhi Agrawal**
Place: Vadodara

ACKNOWLEDGEMENT

I realize that dissertation being a work of cooperation and assistance, it would be far from completion without due acknowledgement of the help gratefully received.

It is my privilege for having an occasion to work under the able and valuable guidance of ***Dr. MALINI MEHTA*** *M.D, (Anaes), Professor, Department of Anaesthesiology, S.B.K.S. Medical Institute & Research Center, Piparia, Vadodara. I express my gratitude for her guiding me on proper lines.*

I am thankful to Dr.Hetal Parikh, M.D., H.O.D, Anaesthesiology,atSmt. B.K. Shah Medical Institute and Research Center, Vadodara, Gujarat, for her continuous supervision and valuable suggestions. Her knowledge and teaching has certainly helped me to mould my concepts towards scientific excellence.

I am grateful to Dr. Mansukhbhai Shah (President), Dr. Dixit Shah (Executive trustee), Dr. M.M. Sattigeri (Registrar), Dr. G.V. Shah (Dean), Dr. Anil Jain (CEO & Medical Superintendent) at Smt. B.K. Shah Medical Institute and Research Center, Vadodara, Gujarat, for providing me the facilities to carry out my dissertation.

I am also indebted to Dr. Rama Upadhayaya (Ex. Prof. & H.O.D.), Dr. Dinesh Chauhan (Professor) Dr. Chinar Hathi (Professor) and Dr. Akhilesh Chhaya (Associate Professor) at Smt. B.K. Shah Medical Institute and Research Center, Vadodara, Gujarat, for their constant support and encouragement throughout the period of study.

I express my deep sense of gratitude to my parents Dr. Harish Agrawal, Dr.Rachana Agrawal and my brother Dr.Rohitashva Agrawal for their continuous support, motivation and sacrifices. The study would not have been possible without them.

I wish to thank my colleagues Dr. Anchal, Dr. Parthav, Dr. Kalidas, Dr. Bansariand junior colleagues Dr. Kushal, Dr.Khushbu, Dr. Sumit, Dr. Pardumanfor their suggestion ,constant encouragement and moral support throughout the period of my study.

I end with a word of gratitude to all my patients for their sincere participation and cooperation.

Dr. Riddhi Agrawal

ABSTRACT

Introduction

The hemodynamic response to laryngoscopy and endotracheal intubation has been recognized since long. These changes in the form of tachycardia, hypertension and arrhythmia may be potentially dangerous. So, the aim of the study was to compare dexmedetomidine1µg/kgand dexmedetomidine 0.5µg/kg for control of hemodynamic changes during endotracheal intubation.

Material and Methods

In this observational study, 60 patients scheduled for elective surgeries under general anaesthesia were divided into two groups **Group D1**(Inj. Dexmedetomidine dose 1µg/kg iv) and **Group D0.5**(Inj. Dexmedetomidine dose 0.5µg/kg iv). Patients belonging to ASA I & ASA II of both sexes, aged 20-60 years, were included in this observational study. Heart rate, blood pressure, ECG were monitored continuously and recorded before giving the study drug, after giving the study drug, at intubation then at1,3,5, 10 minutes after intubation. Data were analysed and $p<0.05$ was considered significant.

Result: Dexmedetomidine group D1 had 4.70% rise in heart rate at time of intubation and group D0.5 had 9.59% rise which was statistically significant($p<0.05$). Except during intubation difference in heart rate between two groups was statistically insignificant.($p>0.05$)

Group D0.5 had significant rise in SBP and DBP during intubation compared to Group D1.Maximum rise in SBP and DBP in Group D0.5 was 14.53% and 12.84%

respectively, whereas in Group D1 it was 5.55% and 8.90% respectively. In Group D0.5, rise in BP lasted longer after intubation compared to Group D1.

There was no significant difference in average thiopentone dose used for induction in both groups. ($p>0.05$)

No side effects of the drug were seen during the study period.

Conclusion: Dexmedetomidine at a dose of 1μg/kg significantly attenuated the sympathetic response of laryngoscopy and intubation whereas dose of 0.5μg/kgalso reduced the pressure response, but its effect was less than that of1μg/kg.

Keywords: Dexmedetomidine, hemodynamic changes and endotracheal intubation.

INDEX

SR.NO.	CONTENTS	PAGE NO.
1.	INTRODUCTION	**1-2**
2.	AIM & OBJECTIVES	**3**
3.	ANATOMY	**4-12**
4.	PHYSIOLOGY	**13-15**
5.	PHARMACOLOGY	**16-25**
6.	REVIEW OF LITERATURE	**26-31**
7.	MATERIALS &METHODS	**32-35**
8.	RESULTS &ANALYSIS	**36-47**
9.	DISCUSSION	**48-53**
10.	CONCLUSION	**54**
11.	SUMMARY	**55-56**
12.	BIBLIOGRAPHY	**57-60**
13.	ANNEXURE	**61-75**
	I – List of Abbreviations II- Proforma III - Informed Consent Form IV - Participant Information Sheet V- Master Chart	

LIST OF TABLES

SR.NO.	TITLE	PAGE NO.
1	Demographic Characters	36
2	Body Weight Distribution	37
3	ASA Physical Status Distribution	38
4	Comparison Of Changes In Mean Heart Rate (HR) Between GroupD1 And GroupD0.5	39
5	Comparison Of Changes In Mean Systolic Blood Pressure (SBP) Between GroupD1 And GroupD0.5	41
6	Comparison Of Changes In Mean Diastolic Blood Pressure (DBP) Between GroupD1 And GroupD0.5	43
7	Comparison Of Changes In Mean Arterial Pressure (MAP) Between GroupD1 And GroupD0.5	45
8	Comparison Of Average Dose Of Thiopentone Between GroupD1 And GroupD0.5	47
9	Side Effects And Complications	47

LIST OF FIGURES

Sr.No.	TITLE	PAGE NO.
1.	Division of Airway	**4**
2.	Blood Supply and Nerve Supply Of Larynx	**8**
3.	Muscles and Cartilages Of Larynx	**9**
4.	Cartilages Of Larynx (Saggital View)	**10**
5.	Cartilages Of Larynx (Posterior Aspect)	**11**
6.	Laryngoscopic View Of Larynx	**12**
7.	Physiology Of Alpha-2 Adrenoceptors	**15**
8.	Chemical Structure Of Dexmedetomidine	**16**
9.	Responses mediated By α-2 Adrenergic Receptors	**17**

LIST OF GRAPHS

Sr.No.	Title	Page no.
1.	Graph Showing Weight Distribution Of Patients In Group D1 and Group D0.5	**31**
2.	Graph Showing ASA Physical Status Distribution In Group D1 and Group D0.5	**38**
3.	Line Diagram Showing Heart Rate At Different Time Intervals between Group D1 and Group D0.5	**40**
4.	Line Diagram Showing Mean SBP At Different Time Intervals between Group D1 And Group D0.5	**42**
5.	Line Diagram Showing Mean DBP At Different Time Intervals Between Group D1 And Group D0.5	**44**
6.	Line Diagram Showing MAP At Different Time Intervals Between Group D1 And Group D0.5	**46**

INTRODUCTION

Laryngoscopy and intubation are associated with intense sympathoadrenal stimulation resulting in hypertension, tachycardia & arrhythmias consequent to the release of catecholamines.[1] The hemodynamic response, being transient in nature may not be of much clinical significance in normal individuals. However, in patients with limited myocardial reserve, tachycardia and hypertension may result in myocardial ischemia, infarction (MI); arrhythmias or precipitate cardiac failure.[2] The hypertensive response may produce deleterious effects in patients with raised intracranial pressures (ICP), intraocular pressures (IOP), pheochromocytomas and vascular lesions such as intracranial arterio-venous malformations or those with aortic aneurysms and dissection[2,3].

Various drug regimens and techniques have been used from time to time for attenuating the stress response to laryngoscopy and intubation, including opioids, barbiturates, benzodiazepines, beta blockers, calcium channel blockers, vasodilators etc.[4,5,6,7,8] The dose of opioids required for effective attenuation of stress response is fairly high and numerous drugs have been used as adjuvants in decreasing the dose of opioids with a varied level of success, but are absolutely not free from side effects[8,9,10]

Alpha-2 adrenergic agonists namely clonidine and dexmedetomidine decrease sympathetic tone and preoperative use of clonidine has been shown to blunt the hemodynamic responses to noxious stimulation and to prevent overall hemodynamic variability[11,12]

Dexmedetomidine is a highly selective alpha-2 receptor agonist having eight times higher affinity and alpha-2 selectivity compared to clonidine and has a shorter duration of action than clonidine.[13,14]

AIMS & OBJECTIVES OF THE STUDY

The observational study was carried out in 60 patients of ASA Physical Status I/II, posted for surgery under general anesthesia.

The study was designed to compare between the two doses of dexmedetomidine 0.5µg/kg and 1µg/kg given over 10 minutes; in terms of:

1. Hemodynamic changes during and after laryngoscopy
2. Reduction in dose of injection Thiopentone.
3. Side effects and complications of dexmedetomidine, if any.

ANATOMY

The airway includes: nasal and oral cavity, pharynx, larynx, trachea and bronchial divisions.

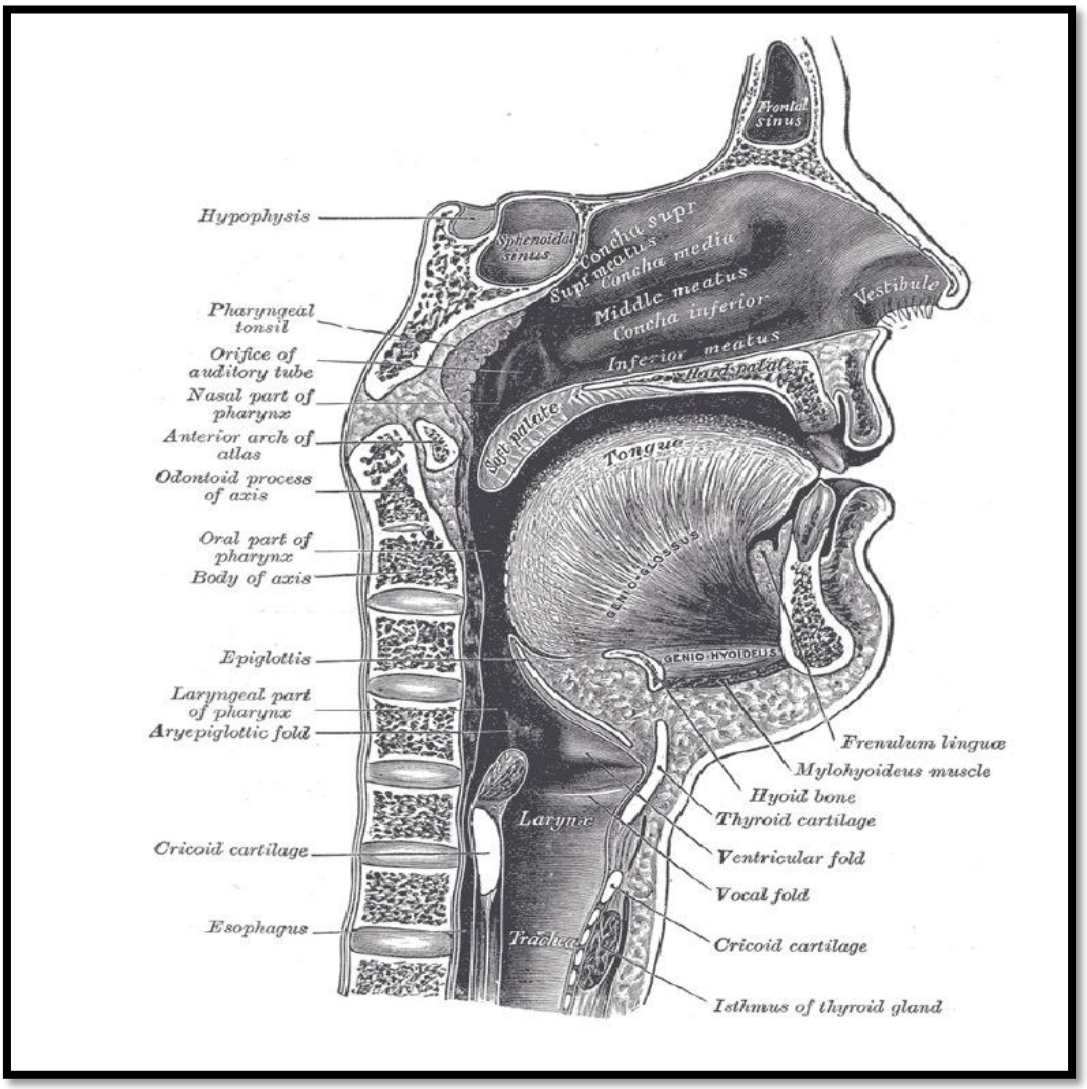


Fig. 1 Division of Airway

Larynx

It is an organ for production of voice. It is situated in between the food and air passages.

Situation and Extent

Larynx lies in the anterior midline of the neck. It extends from the root of the tongue to the lower border of the cricoid cartilage. In adult males it lies in front of 3rd, 4th, 5th and 6^{th} cervical vertebra. But in children and adult females, the level is slightly higher. Until puberty, no differences in the laryngeal size exist between males and females.The female larynx is smaller and more cephalad. The inlet to the larynx is bounded anteriorly by upper edge of epiglottis, posteriorly by fold of mucous membrane stretched between the two arytenoids cartilages and laterally by aryepiglottic folds.

Larynx is made up of skeletal framework of cartilages, connected by joints, ligaments and membranes. The cartilages are moved by various muscles.

The bone of the larynx:

The hyoid bone suspends and anchors the larynx during respiratory and phonatory movements. This is a horseshoe shaped sesamoid bone. It is attached to temporal bone by stylohyoid ligament and to the thyroid cartilage by thyrohyoid membrane and muscles.

The skeleton of the larynx is made up of 3 paired and 3 unpaired cartilages.

Unpaired	**Paired**
1. Thyroid	1.Arytenoid
2. Cricoid	2.Corniculate
3. Epiglottis	3.Cuneiform

Thyroid cartilage

The thyroid cartilage is V shaped in cross section. In females, the sides join at approximately 120° and in males it is closer to 90°. This smaller thyroid angle explains greater laryngeal prominence in males, the long vocal cords, and the lower pitched voice. The thyroid notch lies in the midline at the top of the fusion site of two laminae. On the inner side of this fusion line, are attached the vestibular ligaments and below them, the vocal ligament.

False and true vocal cords

Beneath the laryngeal mucosa, a sheet containing many elastic fibres, the fibro elastic membrane of the larynx and its upper area, the quadrangular membrane, extend in the aryepiglottic fold between the arytenoids and the epiglottis. The lower free border of membrane is called vestibular ligament and forms vestibular folds or false cords.

Cavity of larynx

The cavity extends from inlet of larynx to the lower border of cricoid cartilage. The inlet is bounded anteriorly by the epiglottis, posteriorly by interarytenoid fold of mucous membrane, and on each side by aryepiglottic fold. Within the cavity of larynx there are two folds of mucous membrane on each side, the upper fold is the vestibular fold and the lower fold the vocal fold. The space between vestibular folds is rima vestibule, and between the vocal cords is called rima glottidis. The vocal fold is attached anteriorly to midline of the thyroid cartilage and posteriorly to vocal process of arytenoids cartilage. The rima glottidis is the narrowest part of larynx, in males it is about 23 mm and in females 17 mm in diameter.

The area extending from the laryngeal inlet to the vestibular folds is known as vestibular or supraglottic larynx. The laryngeal space from the free border of cords to inferior border of cricoid is called infraglottic or subglottic space. The region between vestibular folds and vocal cords is termed as ventricle. The ventricle may expand anterolaterally to a pouch like area with lubricating mucous glands called laryngeal saccule. The piriform sinus lies lateral to the aryepiglottic fold within the inner surface of the thyroid cartilage.

SENSORY INNERVATION:

Larynx:

Pyriform fossa, periepiglottic tissue, vallecula and area upto true vocal cords are supplied by superior laryngeal nerve.

Interior surface of vocal cords has sensory innervation from recurrent laryngeal nerve.

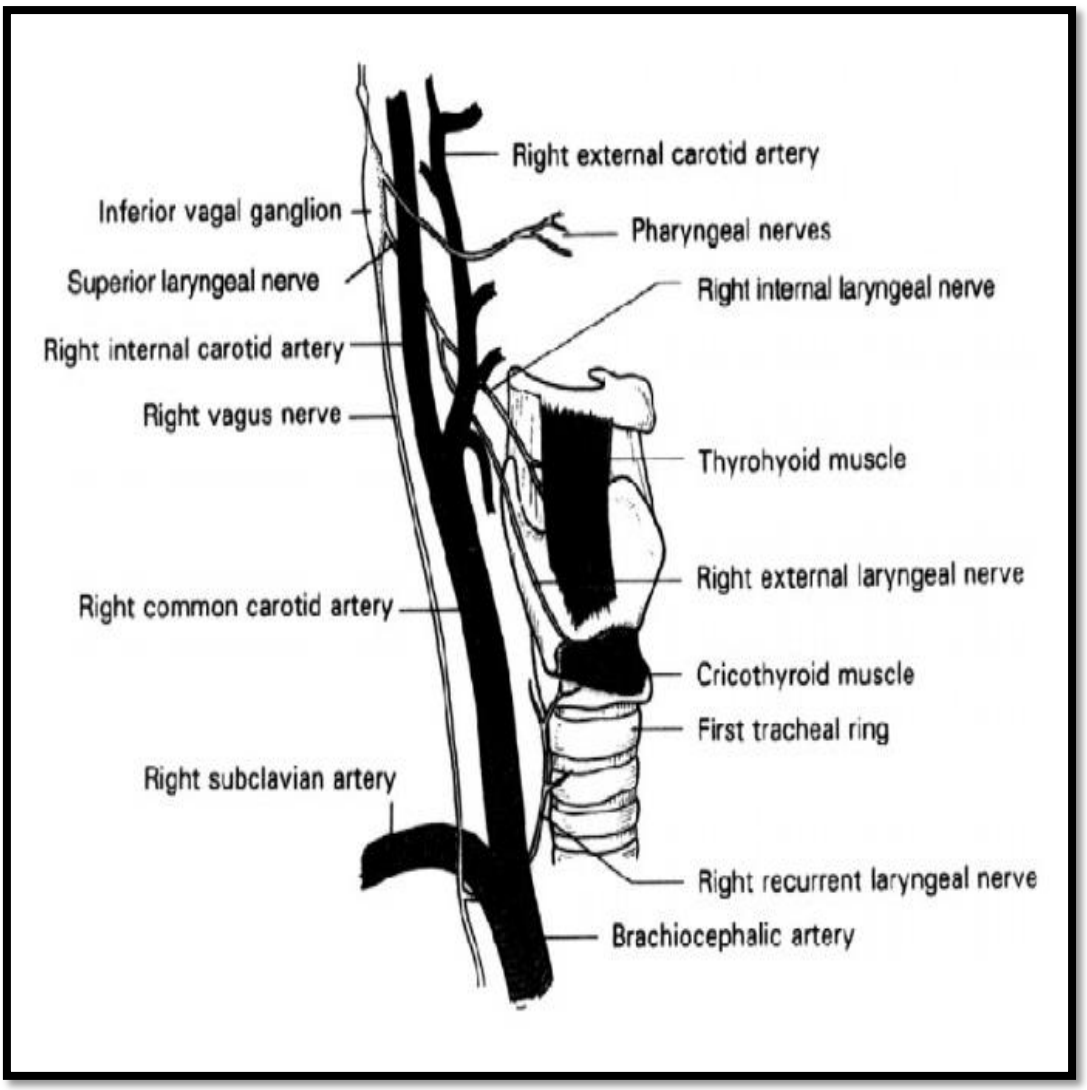


Fig. 2 Blood supply and Nerve supply of larynx

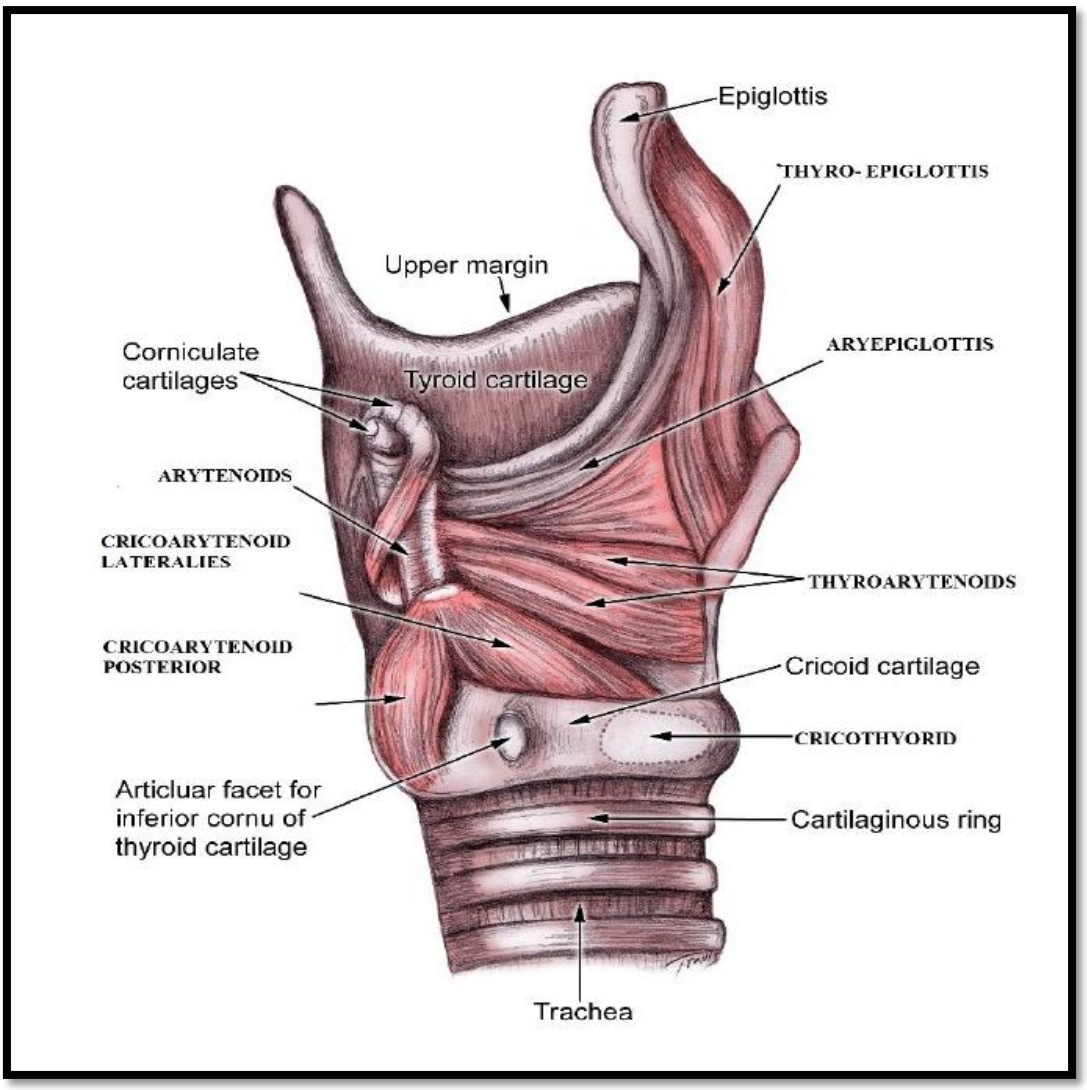


Fig. 3 Muscles and Cartilages of larynx

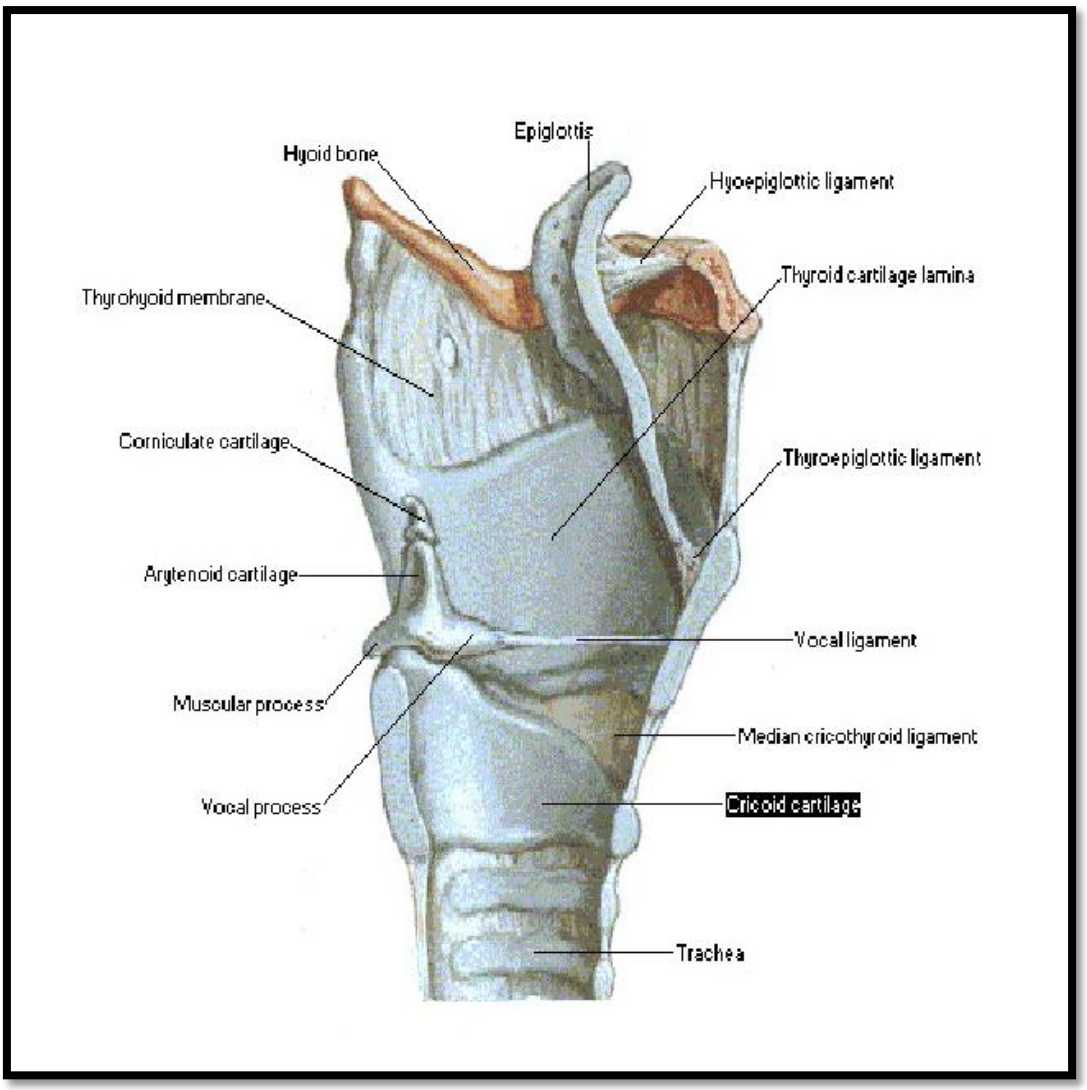


Fig. 4 Cartilages of Larynx (Sagittal)

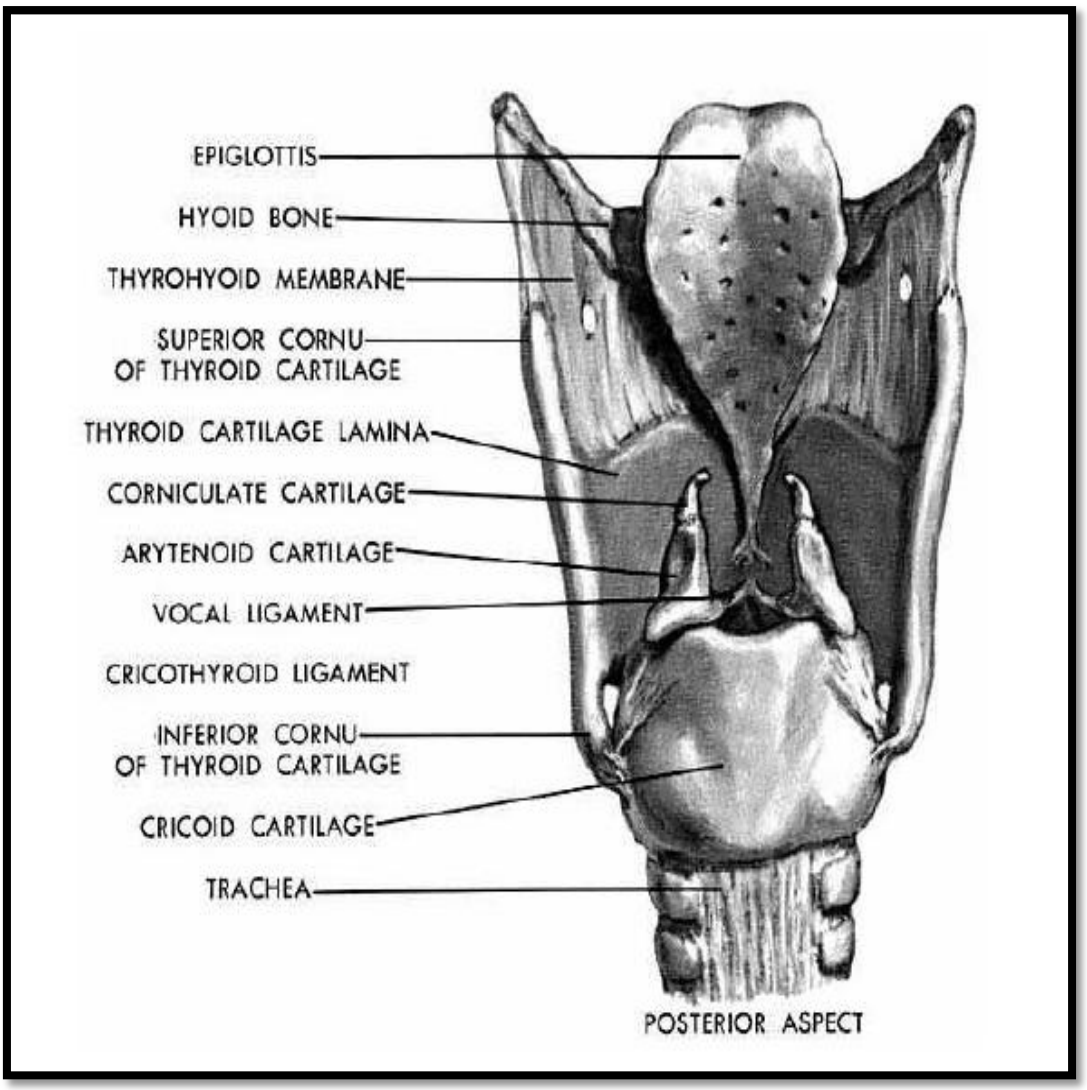


Fig. 5 Cartilages of Larynx (Posterior Aspect)

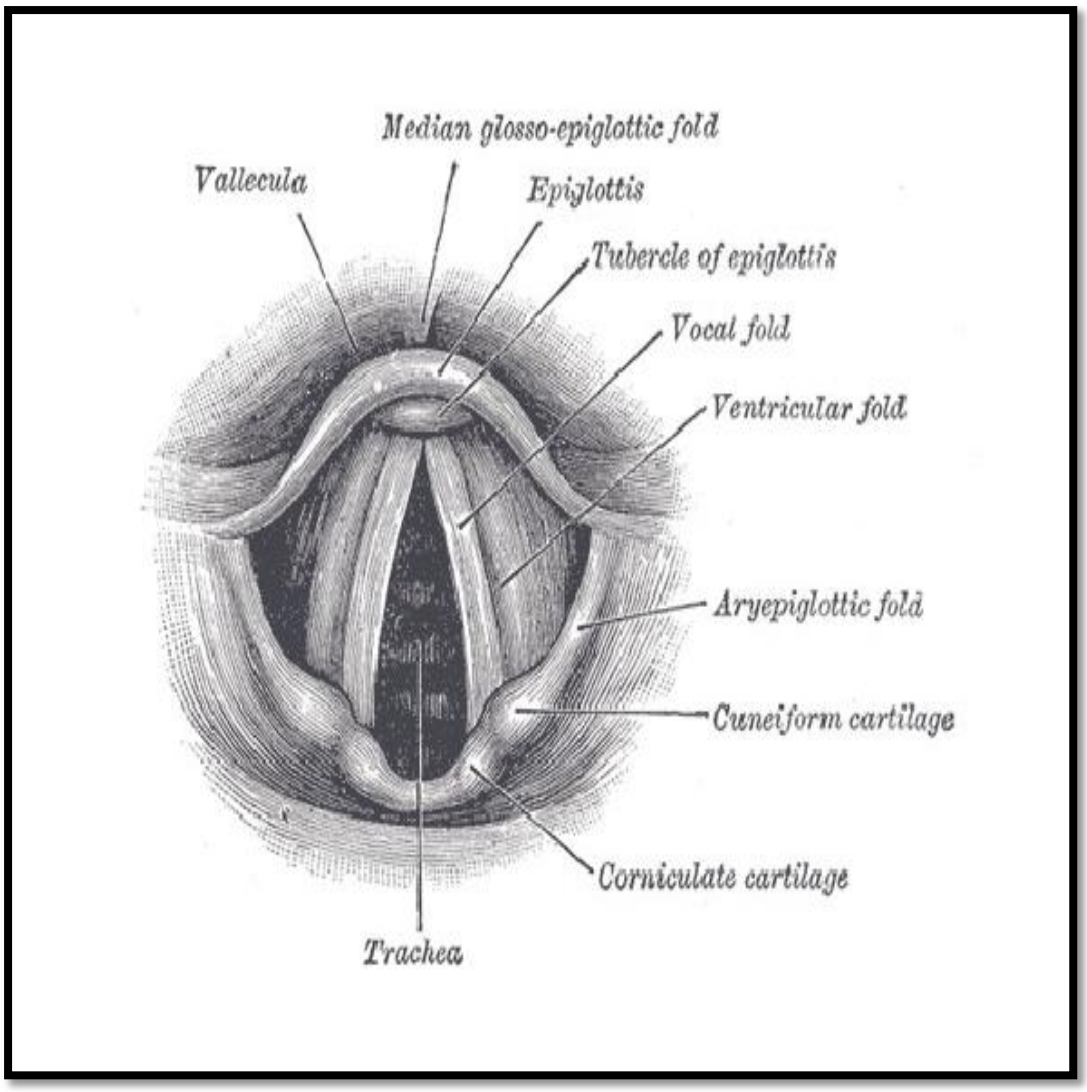


Fig. 6 Laryngoscopic view of larynx

PHYSIOLOGY

Physiology of haemodynamic response to laryngoscopy and endotracheal intubation

Laryngoscopy and endotracheal intubation causes intense reflex increase in heart rate, blood pressure and serum concentration of catecholamines.

The predominant response is tachycardia and arterial hypertension. The latter is due to increased cardiac output rather than increase in systemic vascular resistance and is associated with transient rise in central venous pressure.

Sympatheticinnervation via cardio accelerator fibres from the upper five thoracic segments increases the rhythmicity of sino-atrial node and enhances the rate and force of contraction. Sympathetic system plays a little part in control of heart rate at rest.

The tracheal intubation following laryngoscopy is not only accompanied by increasedsympathetic activity but also increased sympathoadrenal activity. Increased hypothalamic activity and increased traffic in sympathetic efferent tracts are observed. Release of trophic hormones from hypothalamus stimulates release of ACTH, TSH, GH, FSH, LH, and PROLACTIN in addition to ADH from pituitary.

Afferent impulses are carried through trigeminal, Glossopharyngeal, Vagus and sympathetic nerves from the airway. These impulses are relayed in cranial nerve nuclei, vasomotor and autonomic regulatory areas.

The areas that integrate cardiovascular system responses and maintain homeostasis are nucleus solitarius, dorsal vagal nucleus, nucleus ambiguous and parabrachial nucleus.

The nucleus solitarius is the area of primary central synapse for baroreceptor mediated reflexes and relay station for peripheral information to hypothalamic sympathetic control centres. It projects directly to intermediate lateral nucleus of the spinal cord, the common pathway for pre-ganglionic sympathetic outflow. This along with nucleus ambiguous plays an important role in control of secretion of vasopressin .

Different studies have shown rise in mean BP of 25mmhg, 20-40 torr when as compared with awake control levels of 35-60 torr, when compared with pre intubation values and elevation of plasma nor adrenaline and adrenaline by 45% and 40% respectively.

Norepinephrine levels may double from 160 to 300 pg/ml and continue for 4 to 8 minutes. Epinephrine levels may quadruple from 70-280 pg/ml .

Surprisingly increase in plasma noradrenaline concentration and mean arterial pressure of upto 100% and 50% respectively can be correlated but correlation does not exist in the post operative period where noradrenaline concentration can increase upto 200% of the basal value .

Physiology of Alpha-2 Adrenergic Receptors

Alpha-2 receptors are found in many sites throughout the body. They are found inperipheral and central nervous system, in effector organs such as liver, kidney, pancreas, eye,vascular smooth muscles and platelets. Physiologic responses mediated by alpha-2adrenoceptors vary with location and can account for the diversity of their effects.

The classification of alpha-2 receptors based on anatomical location is complicatedsince these receptors are found in presynaptic, postsynaptic and extra

synaptic locations.Theyhave been divided into three subtypes; each type is responsible uniquely for some actions ofalpha-2 receptors. The subtype A, the predominant subtype in CNS, is responsible for thesedative, analgesic and sympatholytic effect; the subtype B, found mainly in the peripheralvasculature, is responsible for the short term hypertensive response and the subtype C, found inCNS, is responsible for anxiolytic effect.[48]

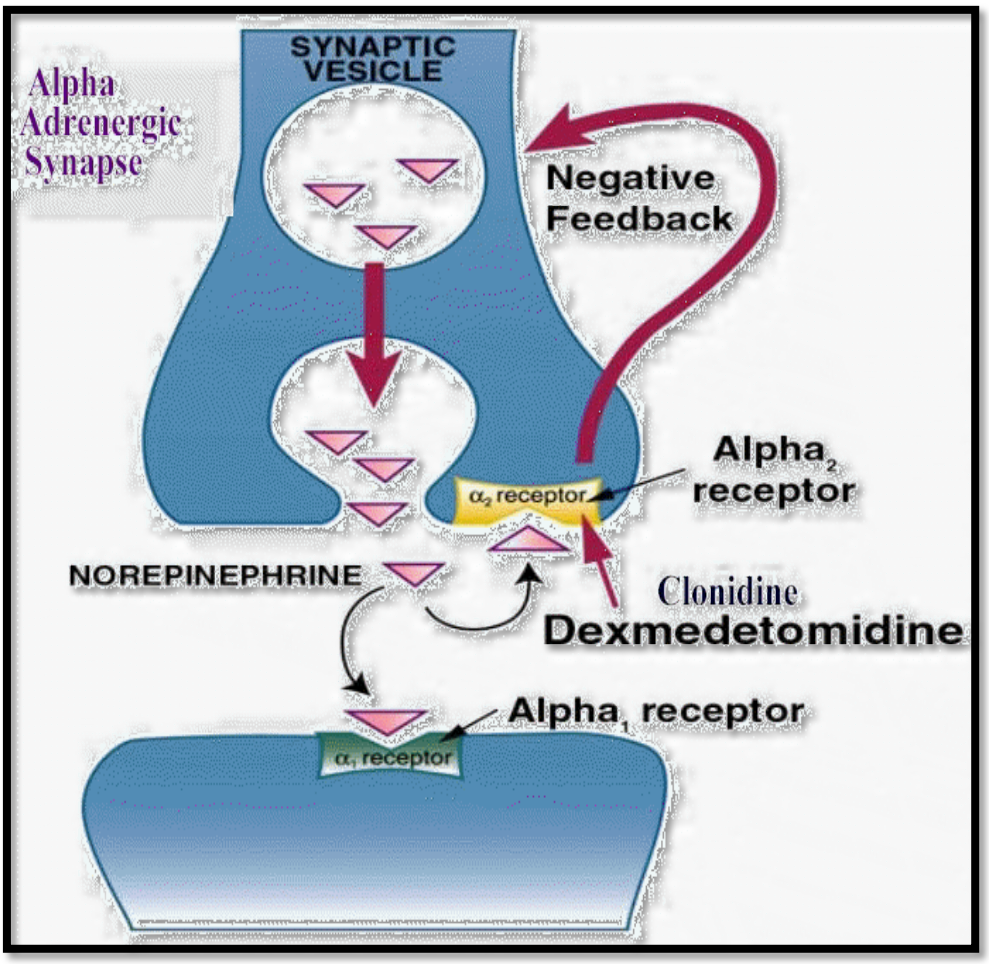


Figure 7: Physiology of alpha-2 adrenoceptors

PHARMACOLOGY

Pharmacology of Dexmedetomidine

Dexmedetomidine hydrochloride, an imidazole compound is the pharmacologically active enantiomer of medetomidine, a veterinary anaesthetic agent. It is described chemically as (+)-4-(s) [2, 3-(dimethyl-phenyl) ethyl]-11-H-imidazole mono hydro chloride. Its empirical formula is $C_{13}H_{16}N_2HCl$ and its molecular weight is 236.7

Structural formula

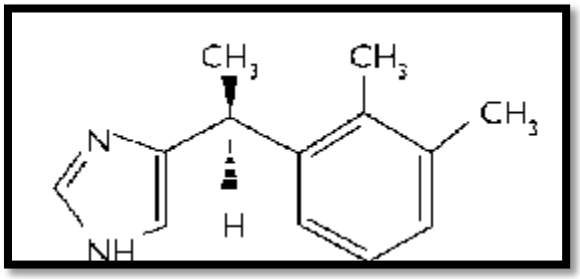


Figure 8: Chemical structure of dexmedetomidine

Physiochemical Properties

A white or almost white powder that is freely soluble in water with Pka of 7.1. Partition coefficient in octanol: water at pH 7.4 is 2.89. Preservative free dexmedetomidine is available in 1 ml and 2 ml ampoule as dexmedetomidine hydrochloride for intravenous use (100µg/ml). It can also be used for intrathecal and epidural anaesthesia.

Mechanism of action

Dexmedetomidine is dextro-enantiomer of medetomidine, with an alpha-2: alpha-1 binding affinity ratio of 1620:1.

Specific alpha-2 receptor subtypes mediate the pharmacodynamic effects of dexmedetomidine. Agonism at alpha-2A receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection and inhibition of insulin secretion. Agonism at alpha-2B receptor suppresses shivering centrally, promotes analgesia at spinal cord sites and induces vasoconstriction in peripheral arteries. Alpha-2C receptors are associated with modulation of cognition, sensory processing, mood and stimulant-induced locomotor activity and regulation of epinephrine outflow from the adrenal medulla.

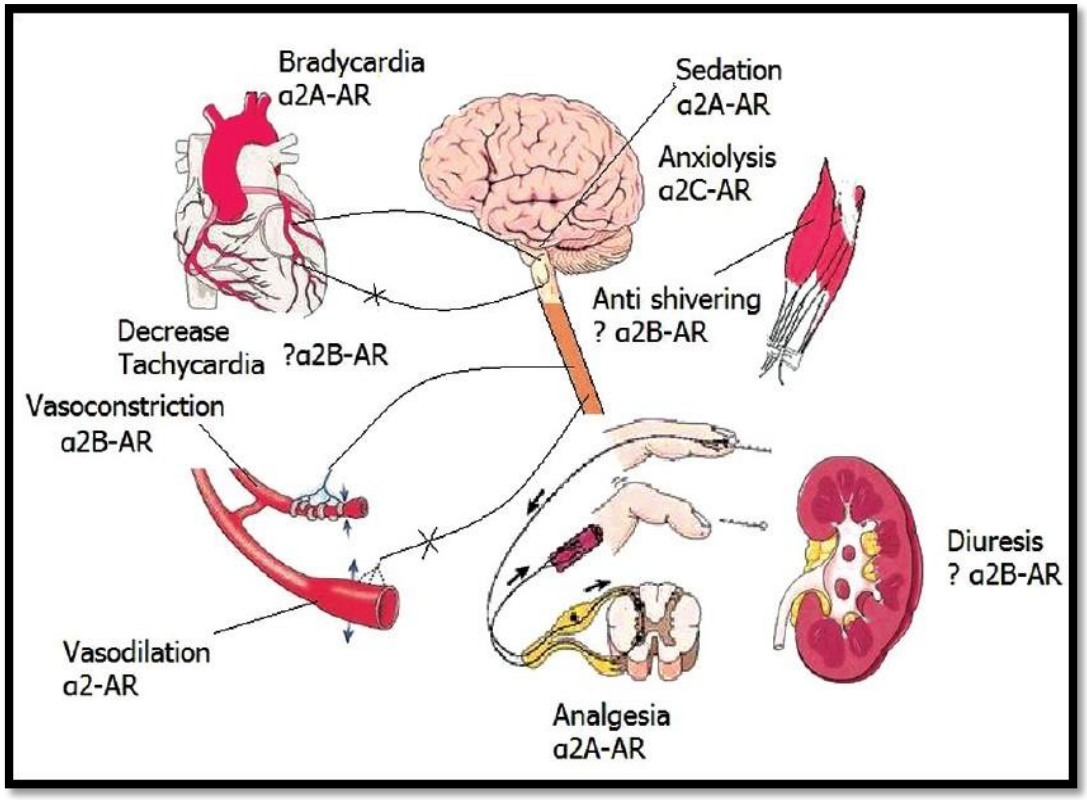


Figure 9: Responses mediated by α-2 adrenergic receptors

The mechanism of action of dexmedetomidine is unique and differs from currently used sedative drugs. Alpha-2 adrenoceptors are found in CNS in highest densities in the locus ceruleus, the predominant noradrenergic nuclei of the brainstem and an important modulator of vigilance. Presynaptic activation of alpha-2A adrenoceptor in the locus ceruleus inhibits the release of nor-epinephrine and

results in the sedative and hypnotic effects. In addition; the locus ceruleus is the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. Stimulation of alpha-2 adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha-2 receptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia.

At the spinal cord, stimulation of alpha-2 receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of release of substance P. Also the alpha-2 adrenoceptors located at the nerve endings have a possible role in the analgesic mechanism by preventing norepinephrine release. The spinal mechanism is the principal mechanism for the analgesic action of dexmedetomidine even though there is a clear evidence for both a supraspinal and peripheral sites of action.

Peripheral Action:

Alpha-2 receptors are located in blood vessels where they mediate vasoconstriction and on sympathetic terminals, where they inhibit norepinephrine release. The responses of activation of alpha-2 receptors in other areas include contraction of vascular and other smooth muscles; decreased salivation and decreased bowel motility in the gastrointestinal tract, inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the kidney, decreased release of insulin from the pancreas, decreased intraocular pressure, decreased platelet aggregation and decreased shivering threshold by 2°C.

Pharmacodynamics

Dexmedetomidine is considered as the full agonist at alpha-2 receptors. The selectivity of dexmedetomidine to alpha-2 receptors compared to alpha-1 receptors is 1620:1. The selectivity is dose dependant at low to medium doses and on slow infusion, high levels of alpha-2 selectivity is observed, while high doses or rapid infusions of low doses are associated with both alpha-1 and alpha-2 activities.

Central nervous system

1. Sedation, anxiolysis, hypnosis and amnesia

Dexmedetomidine provides dose dependant increase in anxiolysis and sedation. The quality of sedation appears to be unique in comparison with gamma-amino butyric acid agents such as Midazolam or Propofol. Stimulation of alpha-2A receptors in the nucleus ceruleus inhibits noradrenergic neurons and inhibits GABAnergic neurons in the ventrolateral preoptic nucleus (VLPO).

The participation of non-rapid eye movement sleep pathways seems to explain why patients who appear to be deeply asleep from dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep. This type of sedation is branded “cooperative or arousable”, to distinguish it from sedation induced by drugs acting on the GABA system, such as Midazolam or Propofol which produce a clouding of consciousness. Sedation with dexmedetomidine is dose dependant, however even low doses might be sufficient to produce sedation.

2. Analgesia

Dexmedetomidine exert analgesic effects at spinal cord level and at supraspinal sites. Dexmedetomidine remarkably decreases opioid requirement.

Dexmedetomidine may also provide antinociception through non-spinal mechanisms. Probable mechanisms are activation of alpha-2A receptors, inhibition of conduction of nerve signals through C and A delta fibres and local release of encephalin.

Respiratory effects

Dexmedetomidine is able to achieve sedative, hypnotic and analgesic effects without causing any relevant respiratory depression unlike opioids. The changes in ventilation appeared similar to those observed during natural sleep. Dexmedetomidine does not cause any changes in arterial oxygenation, pH and respiratory rate. It also exhibits a hypercarbic arousal phenomenon, which has been described during normal sleep and is a safety feature. The obstructive respiratory pattern and irregular breathing are seen with high doses of 1-2 µg/kg given over 2 minutes and are probably related more to deep sedation and anatomical features of the patient and this could be easily overcome by insertion of an oral airway. Co-administration of dexmedetomidine with anaesthetic agents, sedatives, hypnotics or opioids is likely to cause additive effects.

Intravenous or inhaled Dexmedetomidine has been found to block histamine induced bronchoconstriction in dogs.

Cardiovascular effects

Dexmedetomidine does not have any direct effect on the heart. A biphasic cardiovascular response has been described. Administration of a bolus dose of 1 µg/kg body weight, initially results in a transient increase of the blood pressure and a reflex decrease in heart rate. The initial reaction can be explained by peripheral alpha-2B adrenoceptors stimulation of vascular smooth muscles and can be attenuated by a slow infusion over 10 or more minutes.

The administration of a single high dose of Dexmedetomidine reduces norepinephrine release. The release of epinephrine is also reduced .The baroreceptor reflex is well preserved in patients who received dexmedetomidine, and the reflex heart rate response to a pressor stimulus is augmented. These results illustrate that cardiovascular response is evoked mainly by decrease in central sympathetic outflow.

Dexmedetomidine can result in bradycardia and hypotension. These temporary effects can be treated with atropine or ephedrine .

Effect on thermoregulation

Dexmedetomidine suppress shivering, by its activity at alpha-2B receptors in the hypothalamic thermoregulatory center of the brain.

Effects on renal function

"Alpha-2 agonists exert diuretic effect by inhibiting the antidiuretic action of arginine vasopressin at the collecting duct. This result in decreased expression of aquaporin-2 receptors and decreased salt and water absorption."

Organ protective effects

Dexmedetomidine shows neuroprotective effects by several mechanisms. These include sympatholysis, preconditioning and attenuation of ischemic reperfusion injury.

Pharmacokinetics

After intravenous injection, dexmedetomidine has an onset of action after approximately 10 minutes. Peak concentrations are achieved within 1hr after continuous infusion. It has a rapid distribution half-life of 6 minutes and a terminal elimination half-life of between 2 and 2.5 hrs. The drug is highly protein bound (94%) with a 6% free fraction. Dexmedetomidine is rapidly distributed and extensively metabolized in the liver. It undergoes conjugation (41%), n-methylation (21%) or hydroxylation followed by conjugation.

Dexmedetomidine is 94% protein bound and its concentration ratio between blood and plasma is 0.66. The elimination half-life is 2 to 3 hrs with a context sensitive half time ranging from 4 minutes after a 10 minute infusion to 250 minutes after an 8 hrs infusion.

Dexmedetomidine is absorbed systematically through transdermal, buccal or intramuscular routes, with a mean bioavailability from the later 2 routes of 82% and 104% respectively. After intramuscular administration, the time to maximum concentration (T_{max}) in the blood is 1.6 to 1.7 hrs, with an absolute bioavailability of 73%. After transdermal administration, the T_{max} is six hours with an absolute bioavailability of 88%.

Perioperative Uses

1. Pre-medication

Dexmedetomidine has anxiolytic, sedative, analgesic, antisialogogue and sympatholytic properties which render it suitable as a premedication agent. As a premedicant, Dexmedetomidine, at IV doses 0.33 to 0.67 µg/kg given 10 minutes before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia.

a. It reduces thiopental requirements.
b. Reduces the requirements of volatile anaesthetics.
c. More effectively attenuates the haemodynamic responses to endotracheal intubation.
d. Decreases plasma catecholamine concentrations

2. Use of dexmedetomidine for regional anaesthesia

a. Epidural dexmedetomidine at a dose of 100 µg decreased the incidence of postoperative shivering.
b. Intrathecal dexmedetomidine at a dose of 3 µg causes significant prolongation of sensory and motor blockade.
c. Addition of 0.5 µg/kg body weight of dexmedetomidine to lidocaine for intravenous regional anaesthesia improves the quality of anaesthesia and perioperative analgesia.

3. Use in monitored anaesthesia care (MAC). Dexmedetomidine confers arousable sedation with ease of orientation, anxiolysis, and mild analgesia without respiratory depression.

4. Dexmedetomidine has been used as sole anaesthetic agent up to doses of 10 µg/kg/hr.

5. Use of Dexmedetomidine in post-operative period Infusion of dexmedetomidine can be continued in extubated and spontaneously breathing patients. The on-going sedation and sympatholytic effect is beneficial in reducing post-op myocardial ischemic events in high risk patients undergoing non-cardiac surgery.

6. Use of dexmedetomidine in paediatric age group. Addition of dexmedetomidine

   2 µg/kg body weight to bupivacaine for caudal analgesia promotes analgesia after anaesthetic recovery.

7. Use of dexmedetomidine in intensive care unit (ICU)

It provides adequate sedation with minimal respiratory depression and can be used for weaning patients from ventilator.

Side-Effects

Other side effects of dexmedetomidine other than hypotension and bradycardia are hypertension after loading dose, dystonic movements, atelectasis, nausea and vomiting, dry mouth, tachycardia, atrial fibrillation, haemorrhage, acidosis, confusion, agitation and rigors which are rare.

Withdrawal phenomenon is reported after abrupt discontinuation with prolonged administration of dexmedetomidine, leading to development of hypertension, tachycardia, emesis, agitation, dilated pupils, diarrhoea, increased muscle tone and tonic clonic seizures.

Over doses may be treated with the selective alpha-2 antagonist Atipamezole at a dose of 50µg/kg.

Dosage and Administration

The recommended dexmedetomidine dose is an IV infusion bolus of 1 µg/kg body weight over a 10 minute period, followed by a continuous IV infusion of 0.2-0.7µg/kg/hr. The maintenance dose is titrated until the sedation goal is reached. It is not necessary to discontinue dexmedetomidine before, during or after extubation. Dose up to 2.5 µg/kg/hr for up to seven days, with no rebound effect on withdrawal and no compromise in haemodynamic stability have been used in clinical trials.

Drug Interactions

Dexmedetomidine has shown to inhibit CYP2 D6 in vitro, but the clinical significance of this inhibition is not well established. Dexmedetomidine appears to have little potential for interactions with drugs metabolized by the cytochrome p450 system.Co-administration of Dexmedetomidine with sevoflurane, isoflurane, propofol, alfentanil and midazolam may result in enhancement of sedative, hypnotic or anaesthetic effects.

REVIEW OF LITERATURE

1. **Yildiz M,Tavlan A et al**[15]in **2006** evaluated the effect of a single preinduction dose of Dexmedetomidine 1μg/kg body weight on cardiovascular responses resulting from laryngoscopy and tracheal intubation, need for anaesthetic agent & perioperative haemodynamic stability.50 patients scheduled for minor surgery were randomized in two groups,dexmedetomidine group and placebo group,n=25 in each group.During and after drug administration, the Ramsay sedation scale was applied every 5 min,haemodynamic parameters and adverse effects were recorded every 10 min for 1 hour after surgery.The study found out that the dose of thiopentone was decreased by 39% and concentration of Sevoflurane was decreased by 92% during intubation, in dexmedetomidine group compared with placebo group.The increase in BP and HR in dexmedetomidine group was significantly less compared to placebo group.

   They concluded that preoperative administration of a single dose of dexmedetomidine at 1μg/kg resulted in progressive increase in sedation,blunted the haemodynamic responses to laryngoscopy and reduced opioids and anaesthetic requirements.

2. **SagirogluEsraet al**[16]in **2009**, compared the clinical effects of two different doses of Dexmedetomidine on attenuation of haemodynamic responses to laryngoscopy and tracheal intubation.A double blinded,randomized study conducted in 60 ASA I and II patients aged 18-60 years scheduled for elective gynaecological surgery. Two groups of 30 patients each were selected Group 1 patients received Dexmedetomidine 1μg/kg body weight in 10 min and Group 2 patients received 0.5μg/kg body weight in 5 min.They found that HR and BP were significantly

lower in group 1 patients at 60 sec after intubation when compared to group 2.There was no difference between the groups with respect to quality scores of tracheal intubation,position of vocal cords,jaw relaxation and movement of the limbs .

They concluded that Dexmedetomidine 1μg/kg body weight is more effective than 0.5μg/kg body weight in attenuating haemodynamic responses to laryngoscopy and tracheal intubation.

3. **M KeniyaVarshali,et al**[17]in **2011** studied the efficacy of Dexmedetomidine in attenuating symphathoadrenal response to tracheal intubation and analysed reduction in intraoperative anaesthetic requirement.The study was conducted in 60 ASA class I and II patients, divided into two groups of 30 patients each, aged between 18-65 years scheduled for elective surgery of duration of 3 hours or more.Group C received isoflurane-opioid saline anaesthesia, Group D,instead of saline recieveddexmedetomidine in a dose of 1μg/kg body weight over a period of 10min, prior to induction. Dexmedetomidine infusion was continued in a dosage of 0.2-0.7μg/kg/hr till the start of skin closure. There was decrease in the dose requirement of thiopentone by 30%, decrease in isoflurane requirement by 32% and also decrease in fentanyl requirement by 33% in Group D.HR and BP were significantly less in Group D when compared to Group C. Thus, they concluded that perioperative infusion of dexmedetomidine is effective in attenuating symphathoadrenal responses to laryngoscopy and intubation and also has significant anaesthetic and opioid sparing effect.

4. **N Sunil et al[24]**in **2012** carried out a double blinded study to compare the efficacy of IV dexmetomidine 0.5µg/kg and 1µg/kg in obtunding the hemodynamic response to laryngoscopy and endotracheal intubation when administered 10 minutes before intubation. 90 patients scheduled for various elective and emergency surgical procedures under general anesthesia belonging to ASA I and ASA II in age group 18-60 years were divided into 3 groups of 30 each, group 1 received IV NS 20 ml administered over 10 mins, group 2 received IV dex 0.5µg/kg in 20ml NS over 10 mins, group 3 received IV dex 1µg/kg in 20 ml NS over 10 mins.In all the 90 patients anaesthesia was induced 10 minuts after completion of the infusion. The study concluded that Dex 0.5µg/kg significantly attenuates hemodynamic response to laryngoscopy and intubatiom when given for 10 mins, with minimal adverse effects.

5. **In 2012, SulaimanS, et al[18]**designed a prospective , double blinded study to see the efficacy of IV dexmedetomidine for attenuation of cardiovascular responses to laryngoscopy and endotracheal intubation in patients with coronary artery disease.60 patients scheduled for off pump coronary artery bypass surgery were randomly allocated to receive dexmedetomidine 0.5µg/kg or normal saline ,15 minutes before intubation.Patients were compared for hemodynamic changes at baseline,5 minutes after drug infusion, before intubation and at 1,3,5 minute after intubation. The dexmedetomidine group had better control of hemodynamics during laryngoscopy and endotracheal intubation.

6. **NerminGogus et al[19]in 2013**carried a prospective, randomized double blind study to study the effects of dexmedetomidine, fentanyl and esmolol on hemodynamic response in ASA I and II patients. SBP, DBP,MAP,HR at the time

of being admitted at the operation room were recorded. The patients were randomized into three groups: Group I ($n = 30$) received 1 μg/kg dexmedetomidine with infusion in 10 min, Group II ($n = 30$) received 2 μg/kg fentanyl, Group III received 2 mg/kg esmolol 2 min before induction. The patients were then later intubated in 3 min. SBP,DBP,HR,MAP were to be measured before induction, before intubation and 1,3,5 and 10min after intubation. When basal levels were compared with the measurements of the groups, it was found that 5 and 10 minutes after intubation HR in Group I and SBP,DBP,MAP in Group III were lower than other measurements ($p < 0.05$). The study concluded that dexmedetomidine is better to prevent tachycardia. Esmolol has prevented systolic, diastolic, mean arterial pressure increases following intubation. So conslusion was made that more studies are required in order to find a strategy that prevents the increase in SBP and HR

7. **A Laha et al[(20)]in 2014**conducted a study on diminshedsympathoadrenal responses and anesthetic requirement by dexmedetomidine by dividing 50 patients into two groups: Group 1 (n=25): single pre-induction IV dose of dexmedetomidine 1μg/kg and Group 2 (n=25): Control group. The result was that Pretreatment with dexmedetomidine 1 ug/kg diminshed, but was not able to totally replenish the cardiovascular and catecholamine responses to tracheal intubation after induction of anesthesia. HR, SBP, DBP all were increased post intubation at 1,2,3 and 5 minutes in both the groups, but the rise was much less in the dexmedetomidine group

8. **Shirsendu et al[(21)]in 2014etal**conducted a prospective study to compare Dexmedetomidine and Clonidine for reduction of sympathoadrenal responses and

anaesthetic requirements to laryngoscopy and intubation which comprised of 3 groups of 20 (ASA I) patients each. The patients in group I (control) were given normal saline and the groups II and III were given dexmedetomidine (1μg/kg) and clonidine(2μg/kg), respectively. (HR), (SBP), (DBP) and Ramsay sedation score were recorded at 1 and 2 min after completion of administration of study drug. Induction was done with propofol and required dose is noted. HR, SBP, and DBP were again noted during intubation and at 1, 3, 5, and 10 min after intubation.

Authors found that HR, SBP, and DBP all increased during intubation and thereafter in all three groups. Pretreatment with dexmedetomidine 1 μg/kg and clonidine 2 μg/kg diminished the cardiovascular and catecholamine responses to tracheal intubation. Attenuation was much more with the dexmedetomidine group with a quicker return to baseline. Dexmedetomidine was better in terms of anaesthetic requirement (Propofol) and sedative action.

The study concluded that preoperative administration of a single dose of dexmedetomidineat dose of 1μg/kg blunted the hemodynamic responses more than clonidine or placebo during laryngoscopy, and reduced anaesthetic requirements.

9. **Amrutaetal[(25)] in 2016**conducted a study to compare two different doses of dexmedetomidine (1μg/kg or 0.7μg/kg) with regards to their hemodynamic,sedative and analgesic effect in patients undergoing laproscopic surgeries. 84 patients were randomly divided into 2 groups of 42 each . Group A received dexmedetomidine 1μg/kg while group B received 0.7μg/kg as an intravenous bolus dose in 48 ml NS over 15 minutes in preanesthesia room. HR, SBP,DBP,MAP,SPO2,EtCO2, RR, at regular intervals(10,15,30,45,60,75,90,105

and 120 minutes during operation and every 15 minutes for 2hours after extubation).VAS and Ramsay scale were also observed. They concluded that the hemodynamic stability, level of sedation achieved were better with dexmedetomidine 1μg/kg, in patients undergoing laproscopic surgeries, when compared to 0.7μg/kg dose without increase in incidence of adverse effects.

MATERIAL AND METHODOLOGY

The study was conducted after obtaining permission from ethical committee in DhirajHospital, S.B.K.S.M.I.&R.C. in department of anesthesiology. 60 patients of grade I and grade II of American Society of Anesthesiologists classification were allocated in 2 groups (n=30 in each group). The study was observational in nature. All the patients fitting into the inclusion criteria were explained clearly about the purpose and nature of the study in the language they understood. They were included in the study only after obtaining a written informed consent. All the basal parameters and basal vitals were noted at the time of presentation of the patient.

Allocation of Groups:

Total 60 patients were allocated in following two groups:

Group D1 :(n=30) received 1µg/kg body weight of dexmedetomidine over a period of 10 minutes intravenously.

Group D0.5:(n=30) received 0.5µg/kg body weight of dexmedetomidine over a period of 10 minutes intravenously.

Inclusion Criteria

- Age between 18 years &60 years
- ASA-I and II.
- No known history of allergy, sensitivity or other form of reaction to the study drugs
- Patient willing to sign informed consent.
- Mallampatti class I and II

Exclusion criteria

- Patient's refusal.
- ASA III, IV and V.
- Known case of heart blocks, sinus bradycardia and hypotension,autonomic neuropathy.
- Patients on beta blocker drugs
- Mallampatti class III and IV
- Allergy to trial drugs.
- Nasogastric tube insertion
- Patient undergoing procedures requiring head and neck manipulation

Pre-operative Examination

Past and present history of the current complains were taken in detail.General physical examination along with systemic examinations were done. Pulse rate, blood pressure and SpO_2were recorded preoperatively. An assessment of airway was done as per Mallampatti grading. Routine investigations were carried out. Chest X-ray and ECG were done.

Pre-operative Preparation

Tab Alprazolam 0.5 mg was given on the previous nightof surgery and patients were kept nil by mouth after 10p.m. Patients were explained about the procedure of general anaesthesia and a written informed consent was obtained from them. In operation theatre multipara monitor was applied and baseline pulse rate, NIBP, SpO_2 and ECG were recorded. Intravenous line was secured and I.V. fluid was started.

All patients were premedicated with Inj.ondansetrone 0.08mg/kg body weight, Inj.glycopyrrolate 0.004 mg/kg and Inj. midazolam 0.05mg/kg IV .Group D1 Patients were given intravenous dexmedetomidine 1μg/kg body weight diluted in 50 ml normal saline using syringe infusion pump over 10 minutes. Group D0.5 patients were given intravenous dexmedetomidine 0.5μg/kg body weight diluted in 50 ml normal saline, using syringe infusion pump over 10 minutes.

After completion of dexmedetomidine infusion, patients werepreoxygenated with 100% oxygen for 3 minutes.Theywere induced with 2.5% thiopentone 5-7 mg/kg I.V. till the loss of eyelash reflex. Inj .succinylcholine 2mg/kg I.V. was given. After disappearance of fasciculations, patientwas intubated with appropriate sized cuffed endotracheal tube by direct laryngoscopy and attached with anesthesia machine. After checking the equal bilateral air entry endotracheal tube was fixed.Anaesthesia was maintained with oxygen and nitrous oxide(50%-50%), isoflurane and intermittent doses of inj.atracurium I.V. 0.1mg/kg.

Hemodynamic responses were compared in both groups by measuring:

Heart rate (HR) ,Systolic blood pressure (SBP),Diastolic blood pressure(DBP),Mean arterial pressure (MAP) and SPO_2. These parameters were measured at following intervals-

1. Before giving the test drug (base line values)
2. Just before induction of anaesthesia.
3. During intubation
4. At 1 min,3min, 5 min,10 min after intubation.

After the surgical procedure was over , neuromuscular blockade was reversed with Inj. neostigmine 0.05 mg/kg and Inj. glycopyrrolate 0.008mg/kg intravenously. Once all recovery criteria were fulfilled and after oropharangeal suction, trachea was extubated. Patients were monitored in the post operative recovery room for 24 hours .They were observed for analgesia and side effects like nausea, vomiting, sedation, respiratory depression bradycardia and hypotension.

OBSERVATION AND RESULTS

TABLE 1: Demographic Characteristics

	Group D1	Group D0.5	P-value
Age (years)	39.77 ± 2.307	34.27 ± 2.029	0.0786
Weight(kg)	53.27 ± 1.407	55.40 ± 1.659	0.3308
Gender (M/F)	13/17	17/13	
ASA (I/II)	16/14	18/12	

For both age and weight, there was no statistically significant difference in patients of Group D1 and Group D0.5 ($p > 0.05$)

Male to female ratio and ASA grading were uniformly distributed in both groups.

TABLE 2: Body Weight

Body weight	Group D1	Group D0.5
Range	40-74 (kg)	40-75 (kg)
Mean	53.27± 1.407	55.40 ± 1.659

Mean body weight in both the groups was comparable with a minimum weight of 40kg and maximum weight of 74 kg in Group D1 and a minimum weight of 40kg and 75kg in Group D0.5.

Graph 1: Graph showing weight distribution of patients in Group D1 and Group D0.5

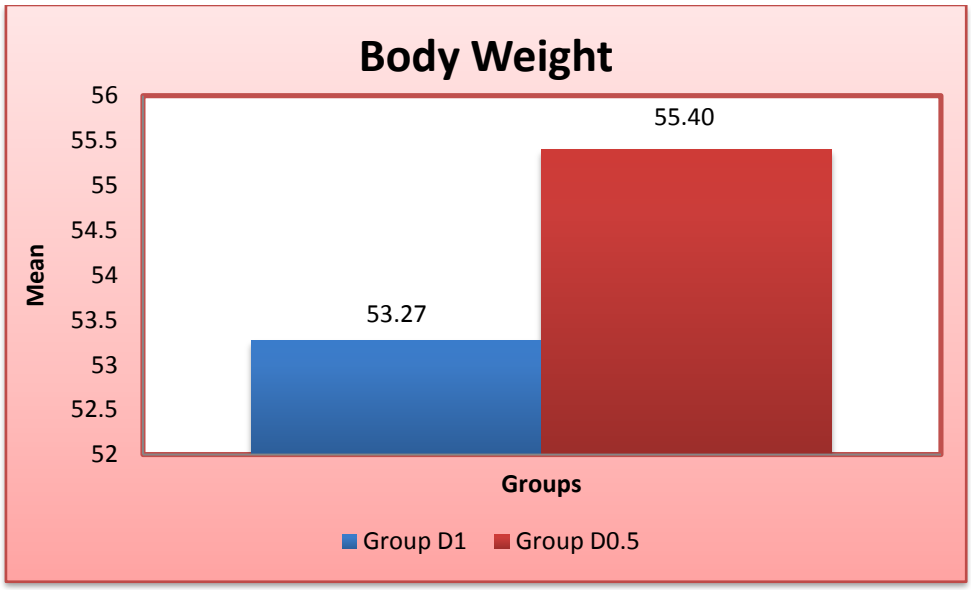


TABLE 3: ASA physical status

ASA Grade	Group D1		Group D0.5	
I	16	53.33%	18	60%
II	14	46.66%	12	40%

Group D1 had 53.33% patients of ASA Grade I and 46.66% patients of ASA Grade II whereas Group D0.5 had 60.00% patients of ASA Grade I and 40.00% patients of ASA Grade-II.

Graph 2: ASA physical status distribution in Group D1 and Group D0.5

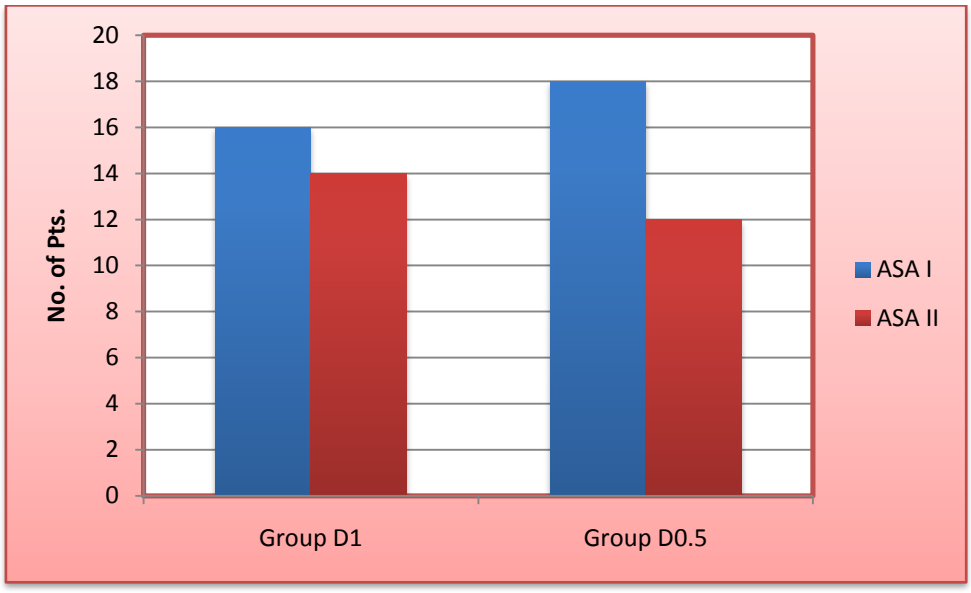


TABLE 4: Comparison of changes in mean Heart Rate (HR) between Group D1 & Group D0.5

Time	Group- D1		Group- D0.5		
	Mean ±SD	**% Change from baseline**	**Mean ± SD**	**%Change from baseline**	**P-Value**
Basal	86.27±1.447	-	86.23±2.027	-	**0.9890**
After study drug	77.00±0.804	**↓10.74**	76.93±0.824	**↓10.78**	**0.9540**
At induction	75.60±1.429	**↓12.36**	77.83±1.714	**↓9.74**	**0.3211**
At intubation	90.33±1.431	**↑4.70**	94.50±0.502	**↑9.59**	**0.0080**
1 min after intubation	86.13±1.276	**↓0.16**	88.50±1.593	**↑2.63**	**0.2509**
3 min. after intubation	84.20±1.517	**↓2.39**	84.30±1.795	**↓2.23**	**0.9662**
5min after intubation	81.73±1.462	**↓5.26**	81.63±1.814	**↓5.33**	**0.9650**
10 min after intubation	79.10±1.892	**↓9.06**	80.40±1.650	**↓6.76**	**0.6065**

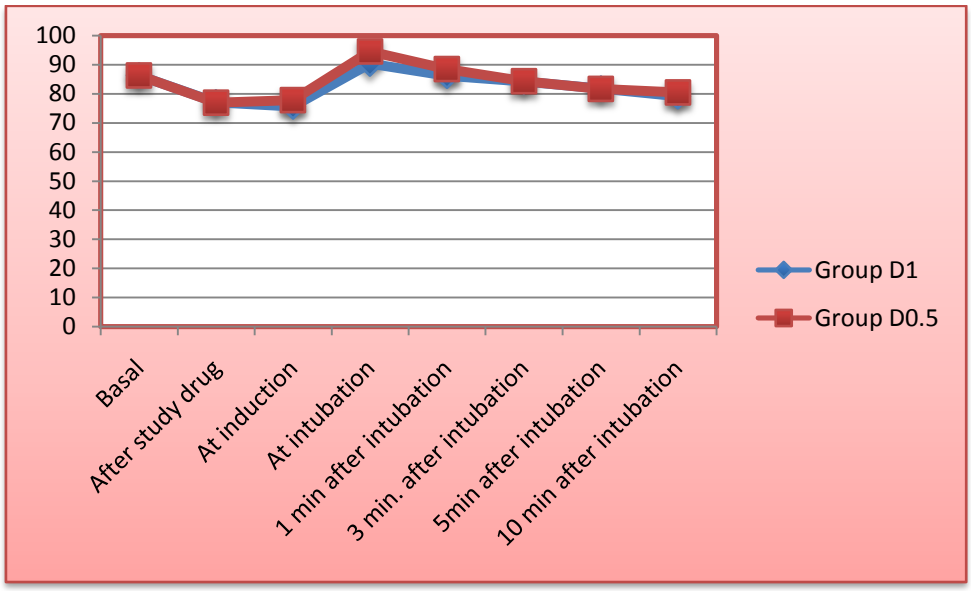
Table shows comparison of changes in Heart Rate (HR) between two groups and intragroup changes in mean heart Rate from basal heart Rate at different time intervals.

Mean HR in Group D1 was 86.27±1.447 per min and in Group D0.5 it was 86.23±2.027 per min at baseline level, which was comparable ($p>0.05$).

There was fall in HR after Dexmedetomidine infusion in both Group D1 and Group D0.5. HR further decreased at induction in both groups .But difference in mean HR between two groups was statistically insignificant ($p>0.05$).Group D1 had 12.36% fall whereas Group D0.5 had 9.74% fall from baseline value

In Group D1 at intubation mean HR increased to 90.33±1.431 per minute showing 4.70% rise ,whereas in Group D0.5 it increased to 94.50±0.502 per min with 9.59% rise. The difference in mean HR between two groups was statistically significant ($p<0.05$)

Graph 3: Showing Heart Rate at different time intervals in Group D1 and Group D0.5



Both groups showed maximum rise in HR during intubation but immediately after intubation it started decreasing. Rate of fall was almost equal in both groups till 5min post intubation.

At 10 min after intubation HR reached to 79.10±1.892 per min in Group D1 with 9.06% fall and in Group D0.5 80.40±1.650 per min with 6.76% fall.

Difference in mean HR between two groups at any time interval was statistically insignificant ($p> 0.05$) except during intubation which was statistically significantly higher in group D1 than in group D0.5 ($p< 0.05$).

TABLE 5: Comparison of changes in mean systolic blood pressure (SBP) between Group D1 & Group D0.5 (in mmHg)

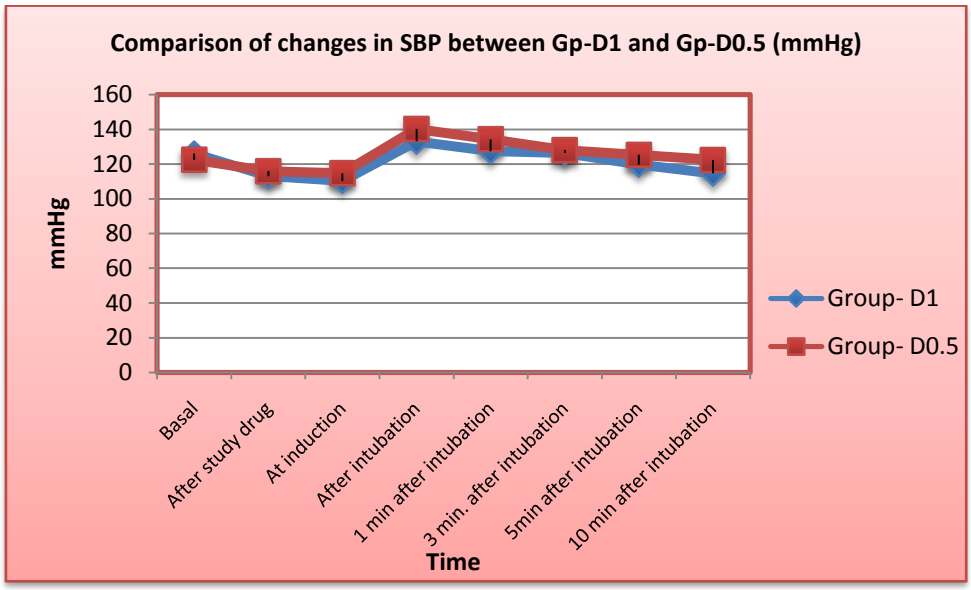
Group- D1			Group- D0.5		
Time	**Mean ±SD**	**% Change from baseline**	**Mean ± SD**	**%Change from baseline**	**P-Value**
Basal	126.10 ± 1.281	**-**	122.50 ±1.189	**-**	**0.0439**
After study drug	113.10 ±2.188	**↓10.30**	115.90 ±1.490	**↓5.38**	**0.0029**
At induction	110.30 ±1.839	**↓12.70**	114.70 ±1.099	**↓6.19**	**0.0445**
At intubation	133.10 ±0.913	**↑5.55**	140.30 ±1.283	**↑14.53**	**<0.0010**
1 min after intubation	127.50 ±1.531	**↑1.11**	134.30 ±1.071	**↑9.63**	**0.0060**
3 min. after intubation	126.50 ±1.844	**↑0.31**	128.10 ±0.991	**↑4.57**	**0.0012**
5min after intubation	119.70 ±1.908	**↓5.07**	125.30 ±0.815	**↑2.28**	**0.0091**
10 min after intubation	114.60 ±1.797	**↓9.12**	122.40 ±1.288	**↓0.08**	**0.0008**

Table shows comparison of changes in mean systolic blood pressure between two groups and intragroup change in mean SBP from basal SBP at different time intervals.

Mean SBP in Group D1 at baseline was 126.10±1.281 mmHg and in Group D0.5 it was 122.50±1.189 mmHg. Baseline SBP between two groups was comparable ($p>0.05$).

There was fall in SBP from baseline value in both groups after study drug infusion and at induction but Group D1 had significant fall (12.70%) compared to Group D0.5 (6.19%). ($p<0.05$)

Graph 4: Mean SBP at different time interval in Group D1 and Group D0.5



Both groups showed maximum rise in SBP during intubation. In Group D1, it increased from 126.10± 1.281mmHg to 133.10± 0.913mmHg (5.55%) whereas in Group D0.5 it rose to 140.30±1.283mmHg from 122.50±1.189mmHg (14.53%). Difference in mean SBP between two groups was statistically highly significant ($p< 0.001$).

SBP in both groups started falling immediately after intubation from its maximum level. In Group D1, at 5 min. after intubation, SBP was below baseline value and even at 10 minutes after intubation, it remained below baseline value, whereas in Group D0.5 SBP remained higher than baseline value and took 10 minutes to reach baseline value.

Difference in SBP from 1 minute after intubation till 10 minutes postintubation was statistically significant ($p< 0.05$).

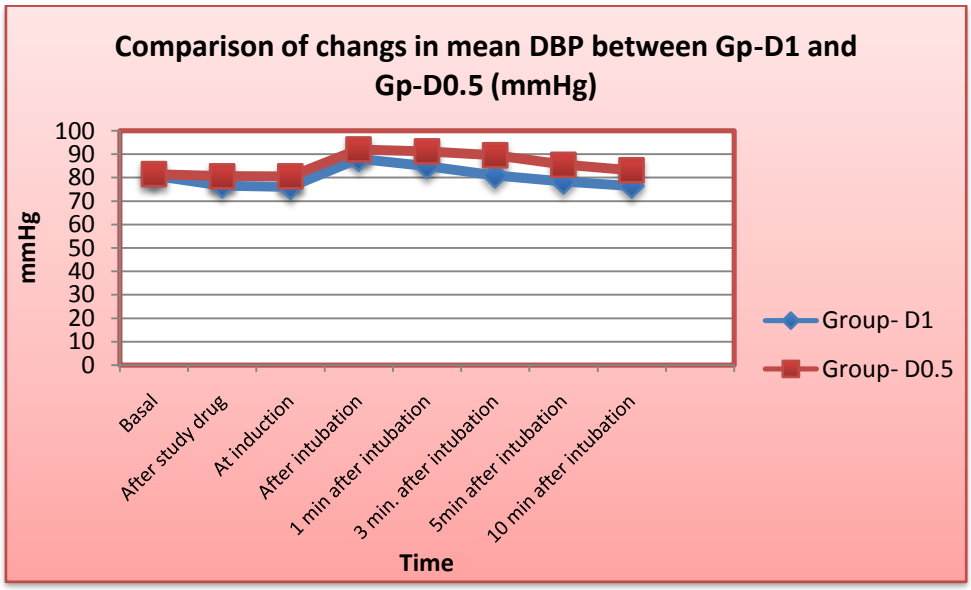
TABLE 6: Comparison of changes in mean diastolic blood pressure (DBP) between Group D1 & Group D0.5 (mmHg)

Group- D1			Group- D0.5		P- Value
Time	**Mean ±SD**	**% Change from baseline**	**Mean ± SD**	**% Change from baseline**	
Basal	80.87±1.679	-	81.53±1.049	-	0.7376
After study drug	76.67±1.082	↓5.19	80.60±0.803	↓1.14	0.0050
At induction	76.07±1.437	↓5.93	80.53±1.015	↓1.22	0.0138
At intubation	88.07±1.270	↑8.90	92.00±0.996	↑12.84	0.0179
1 min after intubation	84.87±1.379	↑4.94	91.20±1.306	↑11.86	0.0015
3 min. after intubation	80.93±1.253	↑0.07	89.60±1.160	↑11.86	<0.0001
5min after intubation	78.33±1.131	↓3.14	85.53±1.129	↑4.90	<0.0001
10 min after intubation	76.53±1.028	↓5.36	83.13±1.137	↑1.96	<0.0001

Table shows comparison of changes in mean diastolic blood pressure between two groups and intragroup changes in mean DBP from basal DBP at different time intervals.

The mean DBP at baseline in Group D1 was 80.87±1.679 mmHg and in Group D0.5 it was 81.53±1.049 mmHg. The difference between two groups was statistically insignificant ($p > 0.05$).

Graph 5: Mean DBP at different time interval in Group D1 and Group D0.5



DBP in both groups decreased after study drug infusion and after induction. The difference was statistically significant ($p < 0.05$).

There was maximum rise in DBP in both groups at intubation. In Group D1 it increased to 88.07±1.270 mmHg from its baseline value showing 8.90% rise whereas in Group D0.5 it went to 92.00±0.996 mmHg from basal DBP with 12.84% rise. This difference was statistically significant ($p < 0.05$).

Immediately after intubation DBP in both groups started decreasing but the rate of fall in DBP in Group D1 was faster compare to Group D0.5 and at 3 min. after intubation DBP in Group D1 was nearly same as baseline value. At 10 min. post intubation DBP was76.53±1.028 mmHg that was 5.36% lower than basal DBP, whereas in Group

D0.5, DBP even at 10 min. after intubation was higher than baseline DBP (83.13±1.137 mmHg).

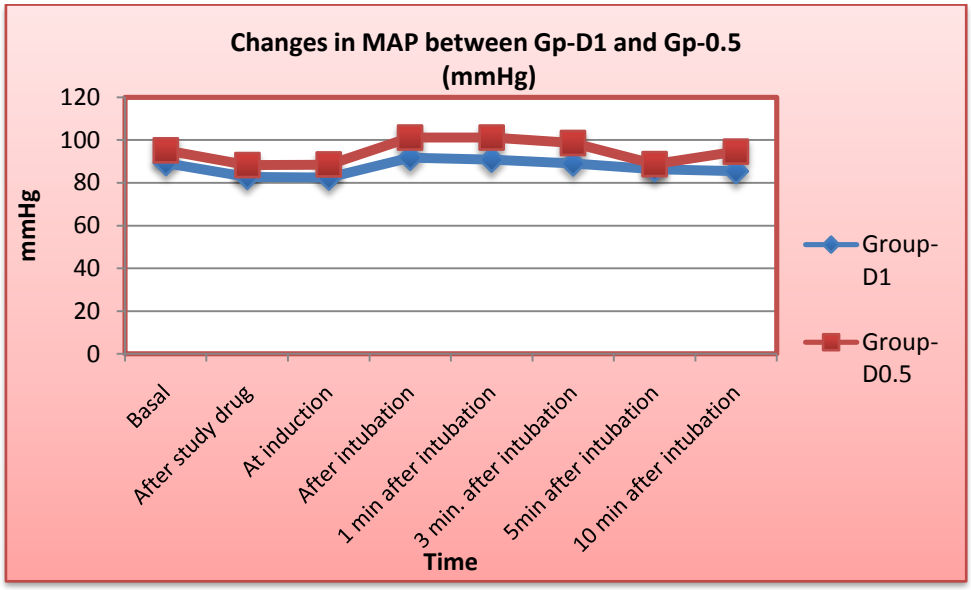
Difference in mean DBP between two groups at any time interval except at baseline was statistically significant ($p<0.05$).

TABLE 7: Comparison of changes in mean arterial pressure (MAP) between Group D1 & Group D0.5

Group- D1			Group- D0.5		
Time	**Mean ±SD**	**% Change from baseline**	**Mean ± SD**	**%Change from baseline**	**P-Value**
Basal	95.94±0.848	-	95.52±0.925	-	**0.0720**
After study drug	88.81±1.436	↓**7.43**	92.36±0.817	↓**3.30**	**<0.0001**
At induction	87.48±1.190	↓**8.81**	91.92±0.823	↓**3.70**	**<0.0001**
At intubation	103.08±1.004	↑**7.00**	108.10±1.290	↑**13.17**	**<0.0001**
1 min after intubation	99.08±0.831	↑**3.20**	105.50±1.206	↑**10.40**	**<0.0001**
3 min. after intubation	96.12±0.910	↓**0.10**	102.43±1.146	↑**7.20**	**<0.0001**
5min after intubation	92.12±0.762	↓**3.98**	98.78±0.923	↑**3.40**	**<0.0001**
10 min after intubation	89.22±0.704	↓**7.00**	96.22±0.855	↑**0.73**	**<0.0001**

Table shows comparison of changes in mean arterial pressure (MAP) between two groups and intragroup changes in mean MAP from basal MAP at different time intervals.

Graph 6: Mean Arterial Pressure at different time intervals between group D1 and Group D0.5



Mean arterial pressure at baseline in Group D1 was 95.94±0.848 mmHg and in Group D0.5 it was 95.52±0.925 mmHg which was comparable (p>0.05).

There was fall in MAP in both groups after study drug infusion and after induction, which was statistically highly significant. (p <0.001).

In Group D1 MAP increased to 103.08±1.004 mmHg during intubation with rise of 7.0% from baseline value whereas in Group D0.5, the rise was 13.17% .The difference was statistically highly significant. (p < 0.0001)

In both groups after intubation MAP decreased from its maximum rise and in Group D1 at 3 min postintubation it reached to baseline level and at 10 min post intubation 7.0% lower than baseline level but in Group D0.5, it remained above basal value even 10 mins after intubation.

Difference in MAP between two groups remained highly significant from time of intubation, till 10 min. after intubation (p< 0.0001).

TABLE 8: Comparison of Average Dose of Thiopentone between Group-D1 and Group-D0.5

	Group- D1	Group- D0.5	p-value
Average dose of thiopentone (mg)	412 .50±26.0	448.30±30.9	0.482

Average dose of Thiopentone used in Group D1 was 412 .5±26.0 mg and in Group D0.5 it was 448.3±30.9 mg. The difference between two groups was statistically insignificant (p>0.05)

TABLE 9: Side effects and complications

	Side effects and Complications	Group D1	Group D0.5
1	Tachycardia	-	-
2	Bradycardia	-	-
3	Hypertension	-	-
4	Bronchospasm	-	-
5	Respiratory Depression	-	-
6	Sedation	-	-
7	Laryngospasm	-	-
8	Cough	-	-

No side effects were seen in any patients of either group.

DISCUSSION

Laryngoscopy and endotracheal intubation are percieved as intense events during general anaesthesia . They give rise to a transient, but marked sympathoadrenalresponse . Therefore controlling this perioperative stress response is pivotal goal of anaesthesiapractise.[22]Various pharmacological& non pharmacological methods were evaluated either in premedication or during induction to alternate these adverse stress responses but no single anaesthetic technique is effective in completely abolishing these responses . The drugs used were either partially effective or were with adverse effects.[23]

Dexmedetomidine offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability by altering the stress induced sympathoadrenal responses to intubation during surgery & during emergence from anaesthesia.

Various authors have employed ivdexmedetomidine for the attenuation of hemodynamic response to endotracheal intubation.

Esra et al[16]in 2009 and Sunil et al[24] in 2012 did two independant studies comparing the effect of dexmedetomidine at two different doses i.e 0.5µg/kg vs 1µg/kg to see the response on attenuation of haemodynamic responses to laryngoscopy & intubation .

In the study of **Esra et al**,1 group of patients received dexmedetomidine at 1µg/kg given over 10 minutes and other group of patients received dexmedetomidine 0.5µg/kg given over 5 minutes, for the patients scheduled for gynecological surgeries.

They concluded that 1µg/kg is better in obtunding hemodynamic response to laryngoscopy.

Whereas **Sunil et al** compared the efficacy of dexmedetomidine 0.5µg/kg and 1µg/kg when administerd over 10 minutes before induction, for the patients scheduled for general surgical procedures. They found that 0.5µg/kg significantly attenuates pressor response to laryngoscopy.

Yildiz et al[15] in 2006 compared dexmedetomidine 1µg/kg with placebo when given over 10 minutes before induction in patients undergoing minor surgical procedures. They also found hemodynamic response to be better in dexmedetomidine group.

Also, **Keniya et al**[17]in 2011 did a study to see the efficacy of dexmedetomidine group when compared with placebo.They similarly administered 1µg/kg dexmedetomidine over 10 minutes and concluded the dose to be effective in blunting the hemodynamic response to laryngoscopy.

Thus, we decided to compare the efficacy of dexmedetomidine at a dose of 1µg/kg with 0.5µg/kg when administered over 10 minutes before induction of anesthesia.

In our study 60 patients were assigned into two groups of 30 each. Group D1 received dexmedetomidine at rate of 1µg/kg and group D0.5 received dexmedetomidine at rate of 0.5µg/kg.Both the doses were given over 10 minutes.

The groups were comparable with respect to demographic factors like age, weight,gender.

Also, baseline heart rate was comparable in both the groups.After 10 minutes of dexmedetomidine infusion, there was fall in heart rate in both the groups which was more in group D1(12.36%) with respect to group D0.5 (9.74%). The fall continued even after induction in both the groups except during intubation.During intubation there was rise in heart rate in both the groups but the rise was less in group D1(4.70%) as compared to group D0.5(9.59%).The difference being statistically significant. ($p<0.05$)

Esra et al similarly observed in their study using dexmedetomidine 1µg/kg,that heart rate was significantly lower post induction of iv anesthetic agent.At 60 second post intubation, the heart rate was significantly lower in dexmedetomidine 1µg/kg.

Our study results were also in accordance with the results of **Keniya et al and Yildiz et al**.They too observed that dexmedetomidine when administered at a dose of 1µg/kg was able to suppress the heart rate response to laryngoscopy.

Yildiz et al found that in both the groups , heart rate increased after intubation, which was significantly lower in dexmedetomidine group 1µg/kg than placebo when the drug was given 10 minutes before induction.

Keniya et alalso concluded in their study that the increase in heart rate after intubation was 21% in placebo group as compared to 7% in group of dexmedetomidine1µg/kg, implying a better hemodynamic response with the drug.

Presynaptic activation of alpha2 adrenoceptor in the locus ceruleus in brain inhibits the release of nor epinephrine. In addition, the locus ceruleus is the site of origin for descending medullospinal noradrenergic pathway,known to be an important

modulator of nociceptive neurotransmitter.Also, postsynaptic activation of alpha2 receptors in the CNS results in decrease in sympathetic activity leading to fall in heart rate.

In our study, SBP, DBP, and MAP were also observed. Baseline SBP was comparable between the two groups. SBP started to fall from baseline after administration of dexmedetomidine till the time of induction, in both the groups. GroupD1 had 12.70% fall as compared to group D0.5 which had 6.19% fall. The difference was significant($p<0.05$). During intubation there was significant rise in SBP in group D0.5 i.e. 14.53% with respect to group D1 which showed a rise of 5.55%. The difference was highly significant($p<0.001$). SBP began to fall post intubation and reached baseline at 3 minutes in group D1 whereas group D0.5 required 10 minutes to reach the baseline.

Similarly DBP in both the groups showed a falling trend till the time of induction, with group D1 showing more fall (5.93%) as compared to group D0.5 (1.22%).The difference was significant. During intubation there was rise in DBP in both the groups.But the rise was much more in group D0.5(12.48%) when compared with group D1(8.90%).Again the difference was significant($p<0.05$). DBP in group D1 reached baseline at 3 minutes after intubation, whereas in group D0.5 DBP remained more than baseline even 10minsafter intubation.

Likewise there was decrease in MAP values in both the study groups after drug infusion and post induction. Group D1 showed 8.81% fall as compared to group D0.5 which showed 3.70% fall.The difference being highly significant. At time of intubation, MAP increased by 7.00% in group D1 whereas it rose by 13.17% in group D0.5. Again the difference was highly significant. ($p<0.001$)

Thus all the three parameters i.e. SBP,DBP and MAP were better managed in the group receiving dexmedetomidine 1µg/kg.

Esra et al similarly observed that SBP,DBP and MAP values were lower post induction in bboth the groups of dexmedetomidine 1µg/kg and 0.5µg/kg, similar to the findings of our study .SBP and DBP were significantly lower at 60 seconds post intubation in dexmedetomidine 1µg/kg as compared to dexmedetomidine 0.5µg/kg.

Yildizet al also observed maximum increase in blood pressure immediately after intubation.During intubation increase in SBP in placebo group was 40% compared to 8% in the group of dexmedetomidine 1µg/kg. Also increase in DBP was 25% in placebo group as compared to 11% in the group of dexmedetomidine 1µg/kg.

Thus the above authors also highlight the blunting effect of dexmedetomidine, showing the dose of 1µg/kg to be more effective than 0.5µg/kg

The initial fall in blood pressure can be explained by peripheral alpha-2B adrenoceptors stimulation of vascular smooth muscles. The initial response is followed by further decrease in blood pressure . Both these effects are caused by inhibition of central sympathetic outflow overiding the direct stimulant effects.

Average requirement of thiopentone was noted during our study. The requirement was 8% less in the group receiving dexmedetomidine 1µg/kg when compared to dexmedetomidine 0.5µg/kg. The difference being not statistically significant. ($p>0.05$)

Similar to our findings, **Bijoykumar panda et al**[(27)]has also observed statistically insignificant reduced requirement of thiopentone in dexmedetomidine group(1µg/kg) as compared to clonidine group (1µg/kg).

Some authors have noted significant reduction in requirement of induction agent. **Aantaa and Coworkers[11],** found 30% reduction in the requirement of thiopentone, while comparing dexmedetomidine 1µg/kg with clonidine 1µg/kg.

Similarly **Keniya et al** reported 30% reduction in the dose of thipentone when they used dexmedetomidine 1µg/kg in their study.

There was no side effect noted in our study.

Similarly, **Shirsedu et al[21]**have also not found any instability of vitals either with clonidine or dexmedetomidine.They compared clonidine at 2µg/kg with dexmedetomidine at 1µg/kg given over 10 minutes, in patients undergoing general surgery.

Keniya et al found bradycardia in only 2 patients out of 60 patients, using dexmedetomidine at 1µg/kg when given over 10 minutes.

Also **Belleville et al[26]**found that dexmedetomidine which was given in 2 minutes at doses of 1-2µg/kg causes irregular ventilation and apnea episodes.Irregular breathing seen with high dose of 1-2 µg/kg probably related to deep sedationn and anatomical features of the patient.

Such side effects were not seen in our study thus making dexmedetomidineat dose of 1µg/kg and 0.5µg/kg when given over 10 minutes to be free of side effects.

CONCLUSION

Based on the present observational study, the following conclusion can be made:

- Dexmedetomidine at dose of 1µg/kg body wt. significantly attenuated the sympathetic response of laryngoscopy and intubation.
- Dexmedetomidine at dose of 0.5µg/kg body wt. also reduced the pressor response, but its effect was lesser than that of dexmedetomidine 1µg/kg.
- Thus this study showed that dexmedetomidine 1µg/kg is superior to dexmedetomidine 0.5µg/kg in the attenuation of hemodynamic response to laryngoscopy and endotracheal intubation with no side effects.
- Dexmedetomidine is helpful in decreasing the requirement of anaesthetic agent for induction.

SUMMARY

An observational study titled **"An observational study to compare the effect of two different doses of dexmedetomidine on haemodynamic response to laryngoscopy and endotracheal intubation"** was carried out at Smt. B.K. Shah Medical Institute and Research Center, Vadodara.

60 patients scheduled for elective surgical procedures under general anaesthesia belonging to ASA Grade I and II, in the age group of 18 to 60 years were included in the study. All 60 patients were divided into two study groups D1 and D0.5, each consisted of 30 patients.

Group D1 patients received dexmedetomidine1 µg/kg iv over 10 min before induction.

Group D0.5 patients received dexmedetomidine 0.5 µg/kg iv over 10 min before induction.

After preoxygenation with 100% oxygen for 3 minutes,anaesthesia was induced with Inj. thiopentone 2.5% till loss of eyelash reflexes and Inj.succinylcholine 2mg/kg was given. Trachea was intubated with appropriate sized endotracheal tube. Pulse, SBP, DBP, MAP were recorded at baseline after study drug infusion, after induction, at intubation, and 1min, 3min, 5min, 10min post intubation. Total dose of thiopentone used for induction was also recorded. All patients were monitored for any side effects.

Dexmedetomidine group D1had 4.70% rise in heart rate at time of intubation and dexmedetomidinegroup D0.5had9.59% rise during intubation which was statistically

significant($p<0.05$). Except during intubation , difference in heart rate between two groups was statistically insignificant.($p>0.05$)

Group D0.5 had significant rise in SBP and DBP during intubation compared to Group D1. Maximum rise in SBP and DBP in Group D0.5 was 14.53% and 12.84% respectively, whereas in Group D1, it was 5.55% and 8.90% respectively. In Group D0.5, rise in BP lasted longer after intubation compared to Group D1.

There was no significant difference in average thiopentone dose used for induction in both groups ($p>0.05$).

No side effects were observed in either of the two groups.

We conclude that iv dexmedetomidine 1µg/kg is better thandexmedetomidine 0.5µg/kg in attenuation of the pressor response of laryngoscopy.

BIBLIOGRAPHY

1. Derbyshire DR, Chmielewski A, Fell D, Vaters M. Plasma catecholamineresponses to tracheal intubation. BJA, 1983; 55: 855-60

2. Fox EJ, Sklar GS, Hill CH, et al. Complications related to pressor response toendotracheal intubation. Anaesthesiology, 1977; 47: 524-25.

3. King BD, Harris LC, et al. Reflex circulatory responses to direct laryngoscopyand tracheal intubation performed during general anaesthesia. Anesthesiology,1951; 12:556-566

4. Charuluxananan S, Kyokong O, Somboonviboon W, Balmongkon B, Chaisomboonpan S. Nicardipine versus lidocaine for attenuating the cardiovascular response to endotracheal intubation. J Anesth 2000;14:77-81.

5. Menda F, Koner O, Sayin M, Ture H, Imer P, Aykac B. Dexmedetomidine as an adjunct to anesthetic induction to attenuate hemodynamic response to endotracheal intubation in patients undergoing fast-track CABG. Ann Card Anaesth 2010;13:16-21.

6. Gunes Y, Gunduz M, Ozcengiz D, Ozbek H, Isik G. Dexmedetomidine-remifentanil or propofol-remifentanil anesthesia in patients undergoing intracranial surgery. Neurosurg Q 2005;15:122-6.

7. Powroznyk A, Vuylsteke A, Naughton C, Misso S, HollowayJ, Jolin-Mellgard A, *et al*. Comparison of clevidipine with sodium nitroprusside in the control of blood pressure after coronary artery surgery. Eur J Anaesth 2003;20:697-703.

8. Abou-Arab MH, Heier T, Caldwell JE. Dose of alfentanil needed to obtain optimal intubation conditions during rapid-sequence induction of anaesthesia with thiopentone and rocuronium. Br J Anaesth 2007;98:604-10.

9. Engoren M, Luther G, Fenn-Buderer N. A comparison of fentanyl, sufentanil, and remifentanil for fast-track cardiac anesthesia.AnesthAnalg 2001;93:859-64.

10. Feld JM, Hoffman WE, Stechert MM, Hoffman IW, Ananda RC. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. J ClinAnesth 2006;18:24-8.

11. Aantaa R, Scheinin M. α-2-adrenergic agents in anesthesiology. ActaAnaesthesiolScand 1993;37:433-48.

12. Quintin L, Bonnet F, Macquin I. Aortic surgery: Effect of clonidine on intraoperative catecholaminergic and circulatory stability. ActaAnaesthesiolScand 1990;34:132-7.

13 Virtanen R, Savola J, Nyman L. Characterization of the selectivity, specifity and potency of medetomidine as an α-2 adrenoceptor agonist. Eur J Pharmacol 1988:9-14.

14. Scheinin H, Virtanen R, MacDonald E, Lammintausta R. Medetomidine-a novel α-2-adrenoceptor agonist: A review of its pharmacological effects. ProgNeuro-PsychopharmacolBiol Psychiatry 1989;13:635-51.

15. Yildize M, Tavlan A, Tuncer S, Reisli R, Yosunkaya A, Otelcioglu. Effect of dexmedetomidine on haemodynamic responses to laryngoscopy and

intubation: perioperative haemodynamics and anaesthetic requirements. Drugs RD 2006; 7(1):43-52.

16. A Sagiroglu, M Celik, Z Orhon, S Yüzer, B Sen. Dıfferent Doses OfDexmedetomidine On Controllıng Haemodynamıc Responses To Tracheal Intubatıon. The Internet Journal of Anesthesiology.2009 ; 27 :2.

17. Varshali M Keniya, SushmaLadi, Ramesh Naphade, " Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement" Indian Journal of Anaesthesia, Vol. 55, Issue 4, July – Aug 2011, 352-357.

18. Sulaiman S, Karthekeyan RB, Vakamudi M, Sundar AS, Ravullapalli H, Gandham R. The effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. Ann Card Anaesth 2012;15:39-43

19. NerminGogus, Belgin Akan, NurtenSerger, Mustafa Baydar et al. The comparison of the effects of dexmedetomidine, fentanyl and esmolol on prevention of hemodynamic response to intubationBraz J Anesthesiol. 2014 Sep-Oct;64(5):314-9.

20. Laha A, Ghosh S, Sarkar S. Attenuation of sympathoadrenal responses and anesthetic requirement by dexmedetomidine. Anesth Essays Res 2013;7:65-

21. ShirsenduMondal, HindolMondal, RitabanSarkar, MusfikurRahaman. Comparison of dexmedetomidine and clonidine for attenuation of sympathoadrenal responses and anesthetic requirements to laryngoscopy and endotracheal intubation.Int J Basic ClinPharmacol. 2014; 3(3): 501-506

22. Kunisawa T, Nagata O, Nagashima M, Mitamura S, Ueno M, Suzuki A, et al Dexmedetomidine suppresses the decrease in blood pressure during anaesthetic induction and blunts the cardiovascular responses to tracheal intubation. Journal of ClinAnaesth 2009; 21:194-9.

23. Sukhminder JS, Kaur J, Singh A, Parmar SS, Singh G, Kulshrestha A, et al Effects of Dexmedetomidine on hemodynamic response to intubation, surgery and extubation and effects on dose of opioids and isoflurane during anaesthesia. Indian Journal of Anaesthesia May 2012:56(2) 123-128

24. Sunil N.,Dhanpal R .The effect of intravenously administered dexmedetomidine on hemodynamic respons to intubation in patients undergoing surgery under general anesthesia.

25. AmruthaS.Pathak ,Jyotsana S. Paranjpe, Ruta H . Kulkarni.Comparision of two doses of dexmedetomidine on hemodynamic stability in patients undergoing laproscopicsurgeries.Journal of krishna institute of medical sciences university. Sep 2016;5(3);40-50

26. Bellevillie JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans in sedation, ventilation and metabolic rate. Anaesthesiology 1992; 77:1134-42.

27. Bijoy Kumar Panda, Priyanka Singh, Sourabh Marne, AtmaramPawar, VarshaliKeniya, SushmaLadi, Sarita Swami. A Comparison study of DexmedetomidinevsClonidine for sympathoadrenal response, perioperative drug requirements and cost analysis. Asian Pacific Journal of Tropical Disease(2012) ;1-6

LIST OF ABBREVIATIONS

ASA	American society of Anaesthesiologists
BMI	Body mass index
Bpm	Beat per minute
CBC	Complete blood count
CVS	Cardiovascular System
CNS	Central Nervous System
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
F	Female
FESS	Functional Endoscopic Sinus Surgery
G	Gauge
GA	General Anaesthesia
HR	Heart Rate
Iv	Intravenous
Inj	Injection
Kg	Kilogram
M	Male
MAP	Mean Arterial Pressure
Min	Minute
Mg	Milligram
µg	Microgram
ML	Millilitre
mm	Millimetres
mmhg	Millimetres of mercury
NIBP	Non-invasive blood pressure

N_2O	Nitrous oxide
NS	Not significant
O_2	Oxygen
ORIF	Open reduction and internal fixation
PACU	Post anaesthesia care unit
RL	Ringer's lactate
SBP	Systolic Blood Pressure
Sec	Second
S/E	Side effects
SGPT	Serum Glutamic Pyruvate Transaminase
Yrs	Years

PROFORMA

Name:	DOA:
Age &Sex:	Weight/Height:
Ward/unit:	Reg. no.:
Preoperative diagnosis:	DOO:
Address:	Operation:

Surgeon: 1)

Pre-Anesthetic Evaluation

Present history

Fever	Drug allergy
Cough	Bleeding disorder
Chest pain	Convulsion
Dyspnoea	Psychiatric/ neurological
Others	Deficit

Past history

Tuberculosis	Ischemic heart disease
Diabetes	Jaundice
Hypertension	Previous operation/

Asthma type of anesthesia

Personal history

Sleep

Bowel &bladder

Appetite

Smoking & alcohol

General Physical Examination

Built and nutrition	Pallor
General condition	Icterus
Level of consciousness	Cyanosis
Temperature:	Clubbing
Pulse:/min	Lymphadenopathy
RR: /min	Edema
BP: mmHg	Spine & Back

Examination of the local site

Airway assessment:

Jaw and Neck movement

Mouth opening:

Oral Hygiene:

Teeth:

Nose:

Systemic Examination

R/ S: P/A:

CVS: CNS:

Relevant laboratory investigations :

CBC:

RBS :

BT :

CT :

Blood Urea :

Serum creatinine :

Urine :

CXR:

ECG:

Baseline Vitals:

Pulse Rate:

Non Invasive Blood Pressure:

SpO_2:

Case has been evaluated and accepted under ASA grade _____ physical status.

Premedications :

Study Groups:

GROUP D1:Inj.Dexmedetomidine at 1µg/kg body weight over 10 mins intravenously.

GROUP D0.5: Inj.Dexmedetomidine at 0.5µg/kg body weight over 10 mins intravenously.

Time	Pulse	SBP	DBP	MAP	SPO2
Basal					
Just before induction					
intubation					
1 min after intubation					
3 min after intubation					
5min after intubation					
10 min after intubation					

Sumandeep Vidyapeeth University

Piparia, Ta. Waghodia, Dist. Vadodara. Pin 391760

Informed Consent Form (ICF) for Participants in Research Programs involving studies on human beings

Study title **: An Observational study to compare the effect of two different doses of Dexmedetomidine for attenuating the haemodynamic response of laryngoscopy and endotracheal intubation**

Study Number: SVU/SBKS/ /2014-____

Participants Initials: _____ Participant's Name _____

Date of Birth / Age _____ (Years)

1. I confirm that I have read and understood the information sheet Dated _____ for the above study and have had the Opportunity to ask questions. [ ]

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

3. I understand that the investigator of this study, others Working on the investigator's behalf, the Ethics Committee And the regulatory authorities will not need my permission To look at my health records, both in respect of the current Study and any further research that may be conducted in Relation to it, even if I withdraw from the study. I agree to This access. However, I understand that my identity will not Be revealed in any information related to third party or published

[ ]

4. I agree not to restrict the use of any data or results that arise

5. From this study provided such a use is only for scientific purpose(s). [ ]

6. I agree to take part in the above study. [ ]

Signature (or thumb impression) of the participants /

Legally acceptable representative _____

Signatory's Name _____ Date _____

Signature of the investigator _____ Date _____

Study Investigator's Name _____

Signature of the impartial witness _____

અભ્યાસ માં ભાગ લેવામાટે સમજી વિચારીને આપેલી પરવાનગી નુ સમ્મતિ-પત્રક

અભ્યાસનુનામ: Laryngoscopy અને endotracheal intubation ના haemodynamic પ્રતિભાવ attenuating માટે Dexmedetomidineના બે અલગ અલગ ડોઝનીઅસરનો એક તુલનાત્મક અભ્યાસ

અભ્યાસ ક્રમાંક:_____ તારીખ:_____

સહભાગીનુપુરુંનામ:_____

સહભાગીનુટુંકુનામ:_____

સહભાગીનીજન્મતારીખ (તા: / /)
ઉંમર: _____

૧.હું ખાત્રી આપુંછું કે મે ઉપરોક્ત અભ્યાસની (તા: / /) માહિતી વાંચી છે અને સમજી છે અને તે અંગેના મુંઝવતા પ્રશ્નો પુછવાની મને તક આપવામા આવીછે.

૨.હું જાણુ છું કે આઅભ્યાસમાં ભાગ લેવો મારામાટે મરજીયાત છે અને,કોઈપણ જાત નુ કારણ આપ્ય વગર, તે માથી ગમેત્યાર ખસીજવાની મનેછૂટ છે, અને આમ કરવાથી મારી તબીબીસારવાર કે કાયદેસર ના હક્કો ને કોઈ અસર નહીં થાય

૩.હું જાણુછું કે આઅભ્યાસ ના તપાસકર્તા તેમના મદદનીશો, એથિકલ ટીમ અને તેના ઉપર દેખરેખ રાખતા અધિકારીઓ ને મારા સ્વાસ્થ્ય ની કોઈ પણ જાતની માહિતી, સદર અભ્યાસને લગતી કે તે સિવાયની, મેળવવા માટે મારી પરવાનગી ની જરૂર રહેશે નહીં, ભલેપછી હું અભ્યાસ માંથી ખસી જાઉં. હું જાણું છું કે મારી આપ્રકાર ની માહિતી અન્ય કોઈ ને જાણ કે પ્રસિધ્ધ નહીં કરવામાં આવે.

૪.આ અભ્યાસ દરમ્યાન, અથવા તેના અંતે પ્રાપ્ત થતી માહિતી, કોઈપણ જાતની વૈજ્ઞાનિક શોધ માટે ઉપયોગ કરવા માટે હું સ્વૈચ્છિક રીતે છુટ આપુંછું

૫. હું આઅભ્યાસ માં ભાગલેવા / જોડાવા માટે સહમતિ આપુંછું.

અભ્યાસમાં ભાગલેનાર ની સહિઅથવાઅંગુઠા નુ નિશાન:_____તારીખ:_____

કાયદેસરના સ્વિકૃતતપાસકર્તાની સહી: _____તારીખ:_____

તપાસકર્તા નુ નામ: _____

તટસ્થસાહેદ / ગવાહનીસહી: _____તારીખ:_____

PARTICIPANT INFORMATION SHEET

Title of the study: . **An Observational study to compare the effect of two different doses of Dexmedetomidine for attenuating the haemodynamic response of laryngoscopy and endotracheal intubation**

Study no: Date:

1. What is the purpose of this study?

To compare the effect of two different doses of Dexmedetomidine for attenuating the haemodynamic response to laryngoscopy and endotracheal intubation

2. Why have I been chosen?

You have been chosen because you meet our required criteria to carry out our study

3. Do I have to take part?

Yes you have to take part in study and by your participation we will be able to compare the effectiveness of our drug

4. How long will the study last?

Study will last for 24 hours.

5. What will happen to me if I take part?

- *Screening Period*
- *Treatment Period*
- *Allocation of investigational product*
- *Follow-up period*

You need not to worry about that. Just before induction you will be given our study drug which will help reduce the stress responses

6. What do I have to do?

You need to cooperate in our study till the end.

7. What is the drug being tested?

Dexmedetomidine

8. What are the benefits of the study?

The study will help us

I. To stabilize haemodynamic responses in patients during laryngoscopy and tracheal intubation.

II. To compare the efficacy and potency of two different doses of Dexmedetomidine in attenuating haemodynamic response to laryngoscopy and endotracheal intubation.

III. To see whether the use of the two different doses make any difference in decreasing requirement of other anaesthetic agents.

9. What are the alternatives for treatment?

Drugs with similar action can be used in place of Dexmedetomidine viz, Clonidine, Esmolol etc

10. What are the side effects of the treatment received during the study?

The most likely adverse effect that can occur is that the patient can have hypersensitivity reaction to the drug or any other minor side effect to drug and these problems will be treated accordingly

11. What if new information becomes available?

If any new information regarding the drug comes in between we will follow the new guidelines.

12. What happens when the study stops?

When the study stops, we will compile the data and statistically analyse the effect of the concerned drug.

13. What if something goes wrong?

There is no harm as such .If anything goes wrong we will investigate and will provide you treatment from our side.

14. Will my taking part be kept confidential?

Yes, patients information will be kept confidential.

15. What else should I know?

You should be assured that the drug which we are using is a well established drug with minimal side effects and by participating in our study, there is no additional risk caused to you.

16. Additional Precautions

Nothing additional precautions required.

17. Whom to call with questions?

Dr .Riddhi Agrawal (mob) : 9727284284

Room no.18, NRI GIRLS HOSTEL, Sumandeep Vidyapeeth, Piparia,

Taluka: Waghodia, District: Vadodara

સહભાગી માહિતી શીટ

આ અભ્યાસના શીર્ષક:. Laryngoscopy અને endotracheal intubation ના હેમોડાયનામિક પ્રતિભાવ ઘટાડવા માટે Dexmedetomidine બે અલગ અલગ ડોઝ અસર એક તુલનાત્મક અભ્યાસ

તારીખ: કોઈ અભ્યાસ:

1. આ અભ્યાસના હેતુ શું છે?

   Laryngoscopy અને endotracheal intubation ના haemodynamic જવાબમાં attenuating માટે Dexmedetomidine બે અલગ અલગ ડોઝ અસર સરખાવવા

2. શા માટે હું પસંદ કરવામાં આવ્યા છે?

   તમે અમારી અભ્યાસ હાથ ધરવા માટે અમારા આવશ્યક માપદંડ છે કારણ કે તમે પસંદ કરવામાં આવી છે

3. મારે ભાગ લેવા માટે હોય?

   હા તમે અભ્યાસમાં ભાગ લેવા માટે હોય છે અને તમારી ભાગીદારી કરીને અમે અમારા દવાની અસરકારકતા સરખાવવા માટે સમર્થ હશે

4. કેવી રીતે લાંબા અભ્યાસ ચાલશે?

   áâBÒâÖ 24 »Ôâ» ¿âÔ×ë.

5. શું મને શું થશે?

   - સ્ક્રિનિંગ પીરિયડ
   - સારવાર પીરિયડ
   - શોધરૂપી ઉત્પાદન ફાળવણી
   - અનુવર્તી સમયગાળા

તમે તે વિશે ચિંતા કરવાની જરૂર નથી. તમે અમારી અભ્યાસમાં ડ્રગ આપવામાં આવશે માત્ર ઇન્ડક્શન પહેલાં તણાવ જવાબો ઘટાડવા મદદ કરશે જે

6. હું શું કરવા છે?

તમે અંત સુધી અમારી અભ્યાસમાં સહકાર માટે જરૂર છે.

7. શું દવા પરીક્ષણ કરવામાં આવી રહી છે?

Dexmedetomidine

8. આ અભ્યાસના શું ફાયદા છે ?

આ અભ્યાસમાં મદદ કરશે

i. Laryngoscopy અને ટ્રેટ્ intubation દરમિયાન દર્દીઓમાં haemodynamic જવાબો સ્થિર કરવા માટે.

ii. Laryngoscopy અને endotracheal intubation માટે haemodynamic જવાબમાં attenuating માં Dexmedetomidine બે અલગ અલગ ડોઝ અસરકારકતા અને ક્ષમતા સરખાવવા માટે.

iii. બે અલગ ડોઝ ઉપયોગ અન્ય એનેસ્થેટિક એજન્ટો જરૂરિયાત ઘટી કોઈપણ ફરક નહીં તે જોવા માટે.

9. સારવાર માટે વિકલ્પો કયા છે?

સરખી ક્રિયા સાથે દવાઓ Dexmedetomidine જેવા, Clonidine, esmolol વગેરે ની જગ્યાએ વાપરી શકાય છે

10. અભ્યાસ દરમિયાન મળેલી સારવારની આડઅસર શું છે?

થઇ શકે છે કે જે મોટા ભાગે પ્રતિકૂળ અસર દર્દી દવા અથવા દવા માટે કોઈપણ અન્ય નાના આડઅસર માટે અતિસંવેદનશીલતા પ્રતિક્રિયા હોઈ શકે છે અને આ સમસ્યા તે મુજબ સારવાર કરી કરશે છે

11. નવી માહિતી ઉપલબ્ધ બને તો?

આ ડ્રગ સંબંધિત કોઈપણ નવી માહિતી વચ્ચે આવે તો આપણે નવી માર્ગદર્શિકા પાલન કરશે.

12. અભ્યાસ અટકે ત્યારે શું થાય?

અભ્યાસ અટકે ત્યારે અમે માહિતી કમ્પાઇલ અને આંકડાકીય રીતે સંબંધિત દવાની અસર પૃથ્થકરણ કરશે.

13. શું કંઈક ખોટું થાય તો?

આવા કંઈપણ અમે તપાસ કરશે ખોટું થાય છે અને તમે અમારી બાજુ માંથી સારવાર આપશે તરીકે કોઈ નુકસાન નથી.

14. મારું નામ ગુપ્ત રાખવામાં આવશે?

હા, દર્દીઓ માહિતી ગુપ્ત રાખવામાં આવશે.

15. બીજું શું જાણવું જોઈએ?

જો અમે ઉપયોગ કરી રહ્યા છો કે જે ડ્રગ ન્યૂનતમ આડઅસરો સાથે સારી ડ્રગ છે કે જે ખાતરી કરવા જોઇએ અને અમારા અભ્યાસમાં ભાગ, તમે કારણ બન્યું કોઈ વધારાના જોખમ છે.

16. વધારાની સાવચેતી?

કંઇ વધારાની સાવચેતી ના જરૂરી.

17. **કોઇપણ પ્રકારની તકલીફ માટેસંપર્ક?**

ડૉ .Riddhi અગ્રવાલ (ટોળું): 9727284284

ઓરડામાં No.18, એનઆરઆઈ GIRLS છાત્રાલય, Sumandeep વિદ્યાપીઠ, Piparia,

તાલુકા: Waghodia, જિલ્લો: વડોદરા

Group D0.5

								HEART RATE (BEATS PER MIN.)								SYSTOLIC BP(mm Hg)								DIASTO		
Sr. No.	Age	Sex	Weight	Date	Operation	ASA Grading	initial dose	HR basal	HR after test drug	HR at induction	HR at intubation	HR 1 min	HR 3 min	HR 5 min	HR 10 min	SBP preop	SBP after test drug	SBP at induction	SBP at intubation	SBP 1 min	SBP 3 min	SBP 5 min	SBP 10 Min	DBP preop	DBP After test drug	DBP at induction
1	31	M	55	#######	Tympanomastoidectomy	I	55	72	72	75	93	85	74	72	72	128	122	120	138	136	130	128	130	80	82	76
2	40	F	69	#######	Hemithyroidectomy	I	69	78	78	70	95	88	81	78	78	128	124	124	146	140	134	122	126	80	84	72
3	22	F	42	#######	Tympanomastoidectomy	II	42	82	82	78	94	88	86	82	83	120	128	120	138	134	130	124	122	90	86	80
4	42	F	65	#######	Hemithyroidectomy	I	65	84	76	74	92	95	87	84	84	130	136	122	142	146	140	134	132	90	88	82
5	35	M	55	#######	Excision	I	55	74	77	69	96	84	76	74	75	130	122	124	136	140	128	126	126	86	82	80
6	30	M	50	#######	Tympanomastoidectomy	II	50	79	75	73	95	85	82	79	80	114	118	116	142	138	124	128	124	70	76	70
7	29	M	60	#######	Mastoidectomy	II	60	110	79	102	93	94	92	95	91	132	126	124	130	134	126	122	118	82	78	74
8	26	M	60	#######	Tympanomastoidectomy	I	60	96	80	92	98	93	91	87	89	128	116	118	132	130	128	128	124	80	76	72
9	36	M	54	#######	Septoplasty	II	54	75	74	71	90	70	78	73	76	110	122	108	144	138	132	130	122	82	80	78
10	20	F	56	#######	Excision	I	56	76	77	75	91	79	68	66	66	120	126	112	136	132	130	122	128	66	70	72
11	50	M	50	#######	Septoplasty with FESS	II	50	104	82	99	97	106	108	103	104	124	112	116	148	140	118	122	130	78	82	80
12	55	M	58	#######	B/L FESS	I	58	92	72	80	91	99	97	92	91	130	118	110	140	134	128	132	124	92	88	90
13	50	M	48	#######	Hemithyroidectomy	II	48	80	71	73	97	86	84	80	76	120	106	108	128	130	124	128	120	80	76	80
14	25	F	70	#######	Reconstruction	II	70	78	83	71	94	89	82	78	71	120	116	114	146	138	128	134	136	82	78	88
15	47	M	75	#######	Resection and Reconstruction	II	75	104	73	91	98	101	103	97	94	120	106	112	144	134	138	132	120	80	82	82
16	33	F	50	#######	Hemithyroidectomy	I	50	100	81	90	99	100	94	98	91	118	108	110	148	132	126	124	124	82	78	80
17	25	M	45	#######	Septoplasty	I	45	81	72	73	93	77	75	72	71	116	110	112	140	130	124	130	128	78	80	84
18	50	M	65	#######	Excision	I	65	98	82	85	97	101	91	93	87	124	116	114	138	136	118	124	122	80	78	84
19	46	M	55	#######	Rhinoplasty	I	55	74	77	66	92	77	68	70	74	128	116	118	134	132	128	122	124	84	86	88
20	45	F	50	#######	Tympanomastoidectomy	II	50	85	71	72	90	91	90	85	81	110	106	110	150	138	124	128	118	78	80	82
21	40	M	40	#######	Hemiglossectomy	II	40	95	83	83	98	83	81	74	77	132	124	126	148	126	122	126	132	86	82	90

22	20	F	55	#######	Septoplasty	I	55	90	79	77	94	87	81	80	79	124	112	114	138	128	122	118	124	82	78	82
23	22	F	50	#######	Excision	I	50	70	75	73	93	75	71	70	69	120	118	120	150	142	136	124	118	82	88	82
24	24	M	60	#######	MRM	I	60	106	70	87	95	99	93	95	91	124	118	110	136	140	128	122	116	80	82	86
25	25	F	70	#######	Tympanomastoidectomy	II	70	88	84	70	92	90	80	72	74	110	102	100	138	136	130	118	114	88	80	76
26	30	F	40	#######	Tympanomastoidectomy	I	40	92	81	83	96	95	96	91	89	116	106	108	144	142	138	118	116	72	80	78
27	23	M	50	#######	Mastoidectomy	II	50	84	73	72	91	89	84	81	77	120	102	112	120	130	128	122	124	86	76	74
28	54	F	50	#######	Hemiglossectomy	I	50	78	77	68	98	81	77	74	72	130	114	112	142	128	126	124	118	90	88	84
29	24	M	50	#######	Mastoidectomy	I	50	80	69	70	94	80	74	72	69	124	114	116	146	124	132	126	112	80	76	88
30	29	F	65	#######	Mastoidectomy	1	65	82	85	73	99	88	85	82	81	124	114	110	148	120	124	122	100	80	78	82

DLIC BP(mm Hg)					MAP (mm Hg)										
DBP at intubation	DBP 1 min	DBP 3 min	DBP 5 min	DBP 10 min	MAP preop	MAP after test dose	MAP at induction	MAP at intubation	MAP at 1min.	MAP 3min.	MAP 5min.	MAP 10min	SpO2	Thiopentone Dose	Complications
90	94	80	86	80	96	95.33	90.67	106	108	96.67	100	96.67	99	475	Nill
94	94	96	88	78	96	97.33	89.33	111.33	109.33	108.67	99.33	94	100	450	Nill
98	98	100	86	76	100	100	93.33	111.33	110	110	98.67	91.33	98	450	Nill
96	102	96	98	96	103.33	104	95.33	111.33	116.67	110.67	110	108	99	475	Nill
92	96	98	94	74	100.67	95.33	94.67	106.67	110.67	108	104.67	91.33	100	450	Nill
82	96	92	96	88	84.67	90	85.33	102	110	102.67	106.67	100	98	400	Nill
98	94	100	84	84	98.67	94	90.67	108.67	107.33	108.67	96.67	95.33	96	450	Nill
92	100	94	86	82	96	89.33	87.33	105.33	110	105.33	100	96	98	450	Nill
100	94	92	88	84	91.33	94	88	114.67	108.67	105.33	102	96.67	100	475	Nill
96	92	90	78	70	84	88.67	85.33	109.33	105.33	103.33	92.67	89.33	97	475	Nill
90	98	92	84	82	93.33	92	92	109.33	112	100.67	96.67	98	99	450	Nill
104	90	92	88	92	104.67	98	96.67	116	104.67	104	102.67	102.67	100	450	Nill
84	100	96	90	84	93.33	86	89.33	98.67	110	105.33	102.67	96	98	350	Nill
90	94	90	82	78	94.67	90.67	96.67	108.67	108.67	102.67	99.33	97.33	100	500	Nill
96	102	96	78	82	93.33	90	92	112	112.67	110	96	94.67	99	500	Nill
92	94	100	80	68	94	88	90	110.67	106.67	108.67	94.67	86.67	98	475	Nill
88	90	86	78	86	90.67	90	93.33	105.33	103.33	98.67	95.33	100	99	425	Nill
94	96	86	88	84	94.67	90.67	94	108.67	109.33	96.67	100	96.67	96	450	Nill
90	90	88	82	86	98.67	96	98	104.67	104	101.33	95.33	98.67	100	400	Nill
92	78	82	84	82	88.67	88.67	91.33	111.33	98	96	98.67	94	99	450	Nill
84	88	90	94	84	101.33	96	102	105.33	100.67	100.67	104.67	100	97	425	Nill

88	78	82	92	90	96	89.33	92.67	104.67	94.67	95.33	100.67	101.33	98	450	Nill
90	90	88	88	86	94.67	98	94.67	110	107.33	104	100	96.67	100	425	Nill
96	88	86	90	88	94.67	94	94	109.33	105.33	100	100.67	97.33	99	475	Nill
86	90	84	74	92	95.33	87.33	84	103.33	105.33	99.33	88.67	99.33	98	450	Nill
88	90	82	84	82	86.67	88.67	88	106.67	107.33	100.67	95.33	93.33	100	450	Nill
84	80	78	92	90	97.33	84.67	86.67	96	96.67	94.67	102	101.33	99	475	Nill
98	78	84	76	84	103.33	96.67	93.33	112.67	94.67	98	92	95.33	100	450	Nill
100	80	84	78	84	94.67	88.67	97.33	115.33	94.67	100	94	93.33	98	400	Nill
88	82	84	80	78	94.67	90	91.33	108	94.67	97.33	94	85.33	99	450	Nill