A STUDY ON THE EFFECT OF DEXMEDETOMIDINE ON HEMODYNAMIC PARAMETERS DURING EXTUBATION IN PATIENTS UNDERGOING ABDOMINAL SURGERY UNDER GENERAL ANAESTHESIA – A PROSPECTIVE RANDOMISED DOUBLE BLIND STUDY

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH - X (ANAESTHESIOLOGY)

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THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY,

CHENNAI

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY ON THE EFFECT OF DEXMEDETOMIDINE ON HEMODYNAMIC PARAMETERS DURING EXTUBATION IN PATIENTS UNDERGOING ABDOMINAL SURGERY UNDER GENERAL ANAESTHESIA – A PROSPECTIVE RANDOMISED DOUBLE BLIND STUDY**" submitted by **DR.K.KALAI SELVI** to the FACULTY OF ANAESTHESIOLOGY, THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY, CHENNAI, in partial fulfillment of the requirement in the award of the degree of M.D., degree Branch X (ANAESTHESIOLOGY) for the MAY 2020 examination is a bonafide research work carried out by him under my direct supervision and guidance.

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MADURAI MEDICAL COLLEGE

MADURAI

CERTIFICATE FROM GUIDE

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INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE

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ENDORSEMENT BY THE DEAN

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DECLARATION

I, **DR.K.KALAI SELVI** declare that the dissertation titled "**A STUDY ON THE EFFECT OF DEXMEDETOMIDINE ON HEMODYNAMIC PARAMETERS DURING EXTUBATION IN PATIENTS UNDERGOING ABDOMINAL SURGERY UNDER GENERAL ANAESTHESIA – A PROSPECTIVE RANDOMISED DOUBLE BLIND STUDY**" has been prepared by me. This is submitted to the Tamil Nadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the award of M.D.Degree Branch X (Anaesthesiology)Degree Examination to be held in May 2020. I also declare that this dissertation, in part or full was not submitted by me or any other to any other to any other university or board, either in India or abroad for any award, degree or diploma.

Date:

Place: Madurai. **DR.K. KALAI SELVI**

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DR.K. KALAI SELVI

CONTENTS

INTRODUCTION

General Anaesthesia is the induction of a balanced state of unconsciousness, accompanied by analgesia and abolition of reflexes.

Intubation with endotracheal tube and extubation are the crucial and important parts during general anesthesia. Tracheal intubation and extubation are accompanied by raised sympathoadrenal activity with an increased plasma catecholamine levels which have effect to increase the heart rate, Myocardial contractility and Systemic vascular resistance.

Majority of patients tolerate these changes without any significant consequences but patients with co-exiting diseases like Hypertension Diabetes and cardiac illness may not tolerated these responses which will increase the heart rate and myocardial O2 demand which may result in Myocardial ischemia.

Various methods are available to attenuate extubation responses which include deepening the plane of anesthesia, topical anesthesia, use of intravenous local anesthetics, calcium channel blockers, opioids and sympathetic blockers etc. Alpha 2-agonists can potentiate the effects of general anesthetics, reduce their dose requirements and

attenuate sympathoadrenal responses to noxious stimuli. Dexmedetomidine is a highly selective Alpha 2 adrenergic agonist. It has sedative, anxiolytic and analgesic actions. It is known to exhibit dose dependent attenuation of the stress response to intubation and extubation.

Administration of 0.5ug/kg of Dexmedetomidine as infusion over 10 min at the time of skin closure will attenuate hemodynamic responses to extubation and provide smooth extubation. It is superior to fentanyl or lignocaine in blunting hemodynamic changes during extubation.

Complications during extubation :

1) Elevated blood pressure
2) Tachycardia
3) Dysarrhythmias
4) Myocardial ischemia
5) Cough
6) laryngospasm
7) Bronchospasm
8) Impaired laryngeal competence
9) Pulmonary aspiration
10) Hypoventilation.

With Dexmedetomidine the Incidence of cough is very low. By reducing the secretions of mucous gland, oral and tracheobronchial gland, the incidence of cough, laryngospasm and broncospasm are decreased.

In this study I am about to evaluate the effect of Dexmedetomidine 0.5ug/kg when given before skin closure, to attenuate the airway reflexes and hemodynamic responses during emergence from anesthesia, providing smooth extubation.

FUNCTIONAL AIRWAY ANATOMY:

The understanding of detailed airway anatomy is essential for the anaesthesiologist to manipulate trachea during airway management. Airway can be divided into upper and lower airways.

1. Upper airway- nasal cavity
   Oral cavity
   Pharynx and larynx
2. Lower airway
   Tracheobronchial tree.

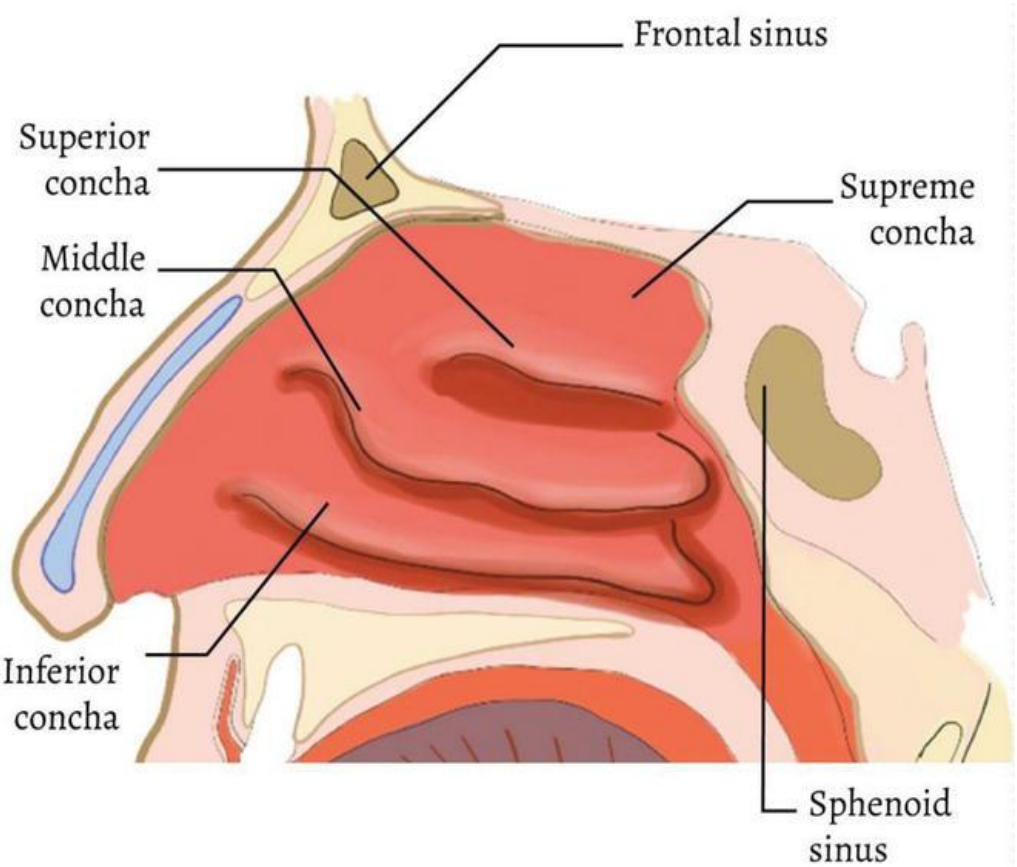
NASAL CAVITY:

Airway begins at the nares. Nasal cavity is divided into right and left nasal passages by nasal septum. Deviated nasal septum is common in adults, so before passing instrument through nasal passage one should know the patency of nasal passage.

The lateral wall is characterized by the presence of 3 turbinates. They divide the nasal passage into 3 scroll shaped meatuses.

Inferior meatus, the space between the inferior turbinate and the floor of the nasal cavity is the preferred pathway for nasotracheal

instrumentation. Roof is formed by cribriform plate which forms a communication between the nasal and intracranial cavities. When there is a fracture of cribriform plate which is a friable structure, the chance for intra cranial instrumentation of endotracheal tube may be there.



Mucosal layer of nasal cavity is highly vascular, so vasoconstrictor has to be applied before instrumentation to avoid bleeding. Posterior openings of nasal passages are the choanae that lead to the nasopharynx.

ORAL CAVITY:

It leads to oropharynx and is bounded by the tongue, hard and soft palate. Anterior 2/3 rd of the roof is formed by hard palate,(maxilla and palatine bones) and posterior 1/3 rd is formed by soft palate (fibromuscular fold of tissue attached to hard palate). Tongue is hold by its extrinsic musculature, among them genioglossus is clinically important which connects the tongue to the mandible. Jaw thrust Maneuver -The sliding component of temparo mandibular joint to move the mandible and the attached tongue anteriorly. This results in avoidance of airway obstruction, caused by the posterior displacement of tongue into the oropharynx.

PHARYNX:

It is a muscular tube extending from the base of skull down to the level of the cricoid cartilage. Posterior pharyngeal wall is made up of buccopharyngeal fascia. Improper placement of the nasogastric tube or tracheal tube leads to laceration of buccopharyngeal fascia and the formation of retropharyngeal dissection. The pharyngeal muscle tone helps to maintain the airway patency in awake patients. One of the primary causes of upper airway obstruction is loss of pharyngeal muscle tone.

The pharynx can be divided into nasopharynx, oropharynx and hypopharynx. Adenoid tonsils are present in the superior and posterior walls of the nasopharynx. They can cause nasal obstruction and when enlarged can cause difficulty in passing airway devices. Nasopharynx which ends at the soft palate is termed as velopharynx which is a common site of airway obstruction.

The Oropharynx starts at the soft palate and extends to the level of epiglottis inferiorly. Palatoglossal and palatopharyngeal folds contain the palatine tonsils that can be hypertrophied and can be caused airway obstruction. The base of the tongue is connected to the epiglottis by the glossoepiglottic fold forming a space called Vallecula.

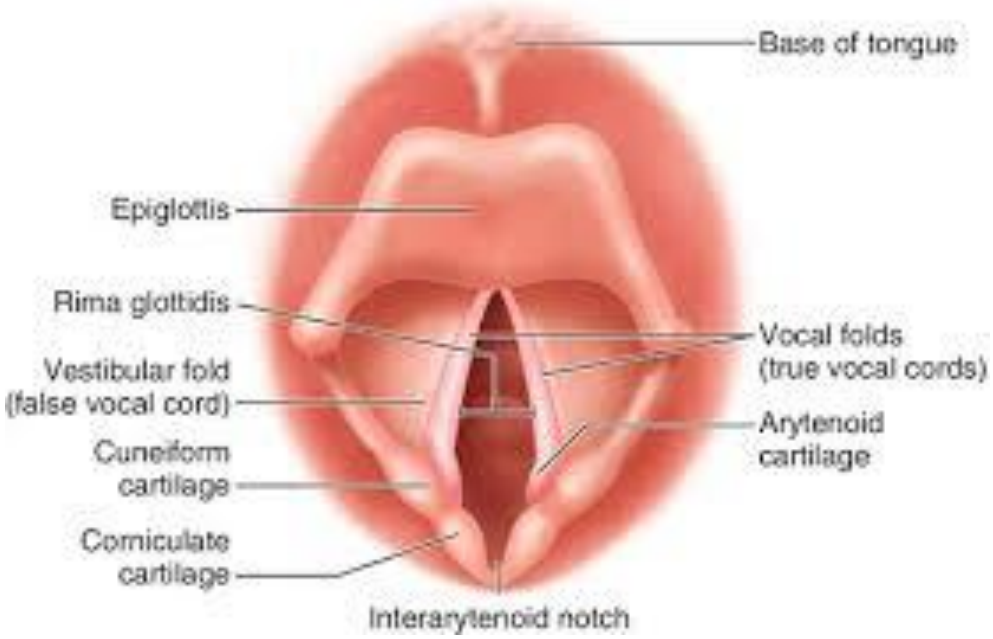
The hypopharynx begins at the level of epiglottis and ends at the level of cricoid cartilage, The larynx protrudes into the hypopharynx, forming two recesses on either side called piriform recesses.

LARYNX:

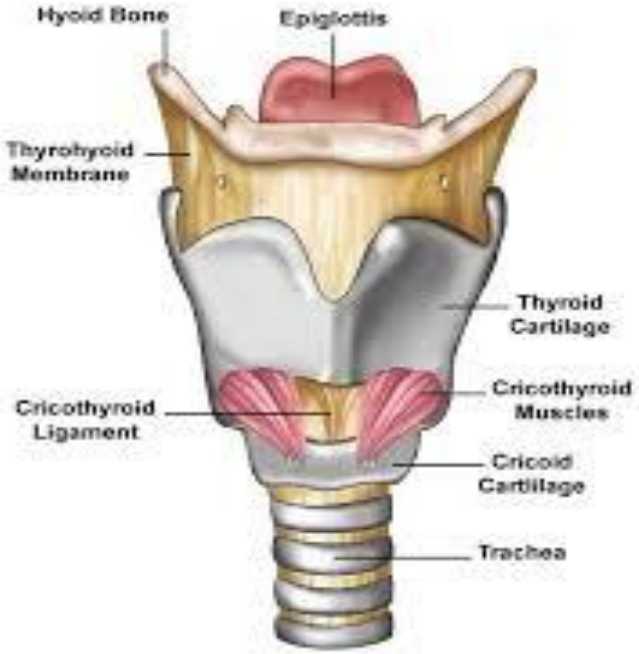
A complex structure containing cartilages, muscles, and ligaments serves as the laryngeal inlet leading to trachea. The important functions are phonation and airway protection. The cartilages include paired arytenoid, corniculate and cuneiform and unpaired thyroid, cricoid cartilages and epiglottis. They are well connected by ligaments, membranes and synovial joints and are suspended by the hyoid bone through the thyrohyoid ligaments and membrane.

Thyroid is the largest one and gives support to the soft tissues of the larynx. Adams apple (superior thyroid notch and associated laryngeal prominence) serves as important landmarks for percutaneous airway techniques and laryngeal nerve blocks. The lower limit of the larynx is the cricoid cartilage at the level of the 6^{th} cervical vertebra and is connected anteriorly to the thyroid cartilage by the cricothyroid membrane.

When viewed from the pharynx ,the larynx begins at the epiglottis during direct laryngoscopy. Laryngeal inlet is bounded by epiglottis anteriorly, aryepiglottic folds laterally and corniculate cartilages and interarytenoid notch posteriorly. Laryngeal cavity is the space inferior to the inlet. The most superior structure within the laryngeal cavity is the vestibular fold, referred to as the vestibular folds or false vocal cords. True vocal cords are situated beneath the false cords. The true cords are attached to the arytenoids posteriorly and the thyroid cartilage anteriorly, where they join together to form anterior commissure. Glottis is the space between the vocal cords, the portion above the glottis is called as the vestibule and the portion inferior to the vocal cords is called as the subglottis.


Base of tongue
Epiglottis
Rima glottidis
Vestibular fold
(false vocal cord)
Cuneiform
cartilage
Corniculate
cartilage
Vocal folds
(true vocal cords)
Arytenoid
cartilage
Interarytenoid notch

LARYNX


Hyoid Bone
Epiglottis
Thyrohyoid
Membrane
Thyroid
Cartilage
Cricothyroid
Muscles
Cricothyroid
Ligament
Cricoid
Cartilage
Trachea

TRACHEA AND BRONCHI

The trachea begins at the cricoid cartilage extending to the carina at the level of the fifth thoracic vertebra. The length is 10 to 15cm in the adult, consisting of 16 to 20 C-shaped cartilaginous rings which open posteriorly. They are joined by fibroelastic tissue and the trachealis muscle forms the posterior wall of the trachea.

At the carina the trachea bifurcates into the right and left mainstem bronchi. The right main bronchus branches off at a more vertical angle than the left one so that more likelihood of foreign bodies and endobroncheal instrumentations.

AIRWAY ASSESSMENT

No single test has been devised to predict a difficult airway accurately 100% of the time. But a complete evaluation of the airway and knowledge of the difficult airway predictors can alert the one to the potential for difficulty and allow for appropriate planning.

Components of the physical examination of the airway

- Visual inspection of the face and neck
- Assessment of mouth opening
- Evaluation of oropharyngeal anatomy and dentition

- Assessment of neck range of motion (assume the sniffing position)
- Assessment of the submandibular space

Assessment of the patient's ability to slide the mandible anteriorly (Test of mandibular prognathism)

PHYSIOLOGIC CONCEPTS FOR AIRWAY MANAGEMENT

1. Preoxygenation
2. Prevention of Pulmonary aspiration of gastric contents by providing premedication
3. Airway reflexes and the physiologic response to intubation of the trachea.

AIRWAY REFLEXES AND THE PHYSIOLOGIC RESPONSES TO INTUBATION OF THE TRACHEA:

The most important function of the larynx is the airway protection, primarily provided by the glottis closure reflex. This reflex is triggered by sensory receptors in the glottis and subglottic mucosa and results in strong adduction of the vocal cords.

Laryngospasm is a potential complication of airway management as it is an exaggerated maladaptive manifestation. Laryngospasm is usually provoked by glossopharyngeal or vagal stimulation due to airway instrumentation or vocal cord irritation in the lighter plane of anesthesia. It can be precipitated by other noxious stimuli and can persist after the removal of the stimulus.

Treatment includes

1. Removal of airway irritants,
2. Deepening of the anesthetic plane
3. Administration of a rapid onset NMBD, such as succinylcholine,

Continuous positive airway pressure (CPAP) with 100% O2 is commonly used as a therapeutic maneuver ,although the pressure may push the aryepiglottic folds closer and may promote laryngospasm by acting as a mechanical stimulus.

4. Bilateral pressure at the laryngospasm notch between the mandibular condyle and the mastoid process (by producing intense painful stimulus-arousing a semiconscious patient and activating autonomic pathways). Tracheobronchial tree also has reflexes to protect the lungs from noxious stimuli.

Irritation of the lower airway by Forein bodies -> Vagal reflex mediated constriction of bronchial smooth muscle -> Bronchospasm. Untreated bronchospasm may produce an inability to ventilate due to severely elevated airway resistance.

Treatment

1.Deepening of anesthetic with propofol or a volatile agent

2.Administration of inhaled b2 agonists

3.Administration of anticholinergic drugs

Endotracheal intubation and laryngoscopy provide an intense noxious stimulus through the vagal and glossopharyngeal afferents that results in a reflex autonomic activation, manifested as hypertension and tachycardia in adults and in infants and small children autonomic activation may result in bradycardia. Hypertension and tachycardia are of short duration, they may have consequences in patients with significant cardiac disease.

AIRWAY MANAGEMENT AFTER THE INDUCTION OF GENERAL ANESTHESIA:

1. Standard intravenous induction with Neuromuscular Blockade
2. Rapid –sequence induction of Anesthesia and intubation of the Trachea
3. Inhalational induction of Anesthesia
4. IV induction with out Neuromuscular Blockade

SURGICAL STRESS RESPONSE:

Surgical stress that associated with major procedures results in profound metabolic and endocrine responses. The combined autonomic, hormonal, and catabolic changes have been called as the surgical stress response. The attenuation of the surgical stress response is beneficial and can lead to improved outcomes.

1. Interruption of the sympathetic response to surgery
2. Use of continuous thoracic epidural infusions of LA –minimize the rise in plasma concentration of catecholamines, cortisol and glucagon.

3. High dose opioids (sufentanil infusion) to reduce the stress response (decrease beta endorphin , Norepinephrine ,Epinephrine, Glucagon , aldosterone,cortisols)

4. Use of perioperative beta blockade(decrease in sympathetic tone)

Perioperative beta blocker therapy when initiated ,it should be titrated to a non-ischemia-inducing HR(usually 60-70beats/min,and not given as a standard fixed dose .Beta –blockers should be continued in patients who already on them as treatment for angina, hypertension, symptomatic arrhythmia. Attempts to discontinue beta blocker resulted in increase the risk of rebound tachycardia and myocardial ischemia.

They should be taken upto the time of surgery. If they have been avoided preoperatively, esmolol or labetolol may be used acutely to attenuate tachycardia and hypertension. Cardioselective and nonselective beta blockers are effective in blocking the chronotropic effects of endotracheal intubation and surgical stress. Early administration of IV beta blocker to patients receiving thrombolytic therapy appears to lower the incidence of ischemia and reinfarction. Also it may reduce the incidence of serious ventricular arrhythmias.

The drugs propranolol, metoprolol, labetlol, esmolol are useful in anesthetic practice. The drugs propranolol, metoprolol, labetalol may be continued if the patient has taken in a long term.

Metoprolol is a cardioselective and lacks intrinsic sympathetic activity and membrane stability activity. Metabolised in the liver by the Monooxygenase system, doses need not be adjusted in the presence of liver failure.Oral dose is 100-200mg/kg for HT and angina .IV dose 2.5 -- 5mg every 2 to 5 min upto 15mg,with titration to HR and BP.

Labetolol is a competitive antagonists at the alpha 1 and beta adrenergic receptors consisting of 4 isomers that block the alpha1,beta1 and beta 2 receptors . It can inhibit neuronal uptake of Norepinephrine,can act as a partial agonist at beta2 receptors.Oral dose is 200 - 400mg twice daily, metabolished by the liver. IV dose 5 - 10mg every 5 min up to a 2mg/min infusion. It significantly attenuates cardiovascular responses to endotracheal intubation.

Esmolol has a uniquely short half life of 9 to 10 mins that makes it useful in anaesthetic practice, because of its hydrolysis by esterases. The peak effect of its loading dose are seen within 5 to 10 mins and diminish rapidly within 30 mins. It is cardioselective and may be

given as bolus of 0.5 mg / kg to attenuate cardiovascular responses to endotracheal intubation. It is safe and effective for the treatment of intraoperative and postoperative hypertension and tachycardia. It has been used safely even in patients with compromised LV function.

AUTONOMIC NERVOUS SYSTEM:

FUNCTIONAL ANATOMY:

The sympathetic nervous system is an amplification response ,and the parasympathetic system is a discrete and narrowly targeted response. The enteric nervous system is arranged nontopographically and relies on the mechanism of chemical coding to differentiate among nerves serving different functions

Sympathetic nervous system originate from the spinal cord in the Thoracolumbar region(T2 to L2 or 3)The preganglionic nerve fibers extend to 3 types of ganglia as paired sympathetic chains, unpaired distal plexuses ,terminal or collateral ganglia near the target organ.

The preganglionic fibers leave the SC in the Anterior nerve roots, enter the ganglia ,leaving the ganglian, postsynaptic fibers reenter the Spinal nerve and then innervate the pilomotor and

sudomotor effectors and blood vessels of the skeletal muscle and skin . Sympathetic postganglionic fibers innervate the trunk and limbs through the spinal nerves.

The sympathetic distribution to the HEAD and NECK mediates vasomotor, pupilo dilator, secretory and pilomotor function comes from three ganglia of the cervical sympathetic chain. The unpaired prevertebral ganglia reside in the abdomen and pelvis anterior to the vertebral column and are the celiac, superior mesenteric ,aorticorenal,and inferior mesenteric ganglia. postganglionic fibers from synaptic links of the upper thoracic sympathetic fibers in the paravertebral ganglia form the terminal cardiac, esophageal ,and pulmonary plexuses. The postganglionic fibers from these plexues innervate the viscera of the abdomen and pelvis.

Ganglia of the third type, the terminal or collateral ganglia are small and near their target organs (adrenal medulla)The adrenal medulla and other chromaffin tissues are homologous to the sympathetic gangia, derived from neural crest cells. Unlike the sympathetic postganglionic fibers the adrenal medulla , releases epinephrine and norepinephrine.

PARASYMPATHETIC NERVOUS SYSTEM :

Parasympathetic nervous system arises from cranial nerves III, VII, IX, and X as well as sacral segments. Ganglia of the parasympathetic are in close proximity to or within the innervated organ, making more targeted and less robust than the sympathetic nervous system. Preganglionic fibers originate in three areas, the midbrain , medulla oblongata, sacral part of spinal cord.

The vagus is the most important of the parasympathetic nerves and transmits fully 75% of the traffic of the parasympathetic nervous system.it supplies the heart ,tracheobroncheal tree , liver, spleen, kidney and entire gastrointestinal tract except for the distal part of the colon. The preganglionic fibers of the vagus are long and the postganglionic fibers are short . The vagal innervation of the Auerbach plexus may connect 1 nerve fiber to 8000 cells.

The 2^{nd} through 4^{th} sacral segments contribute the nervi erigentes or the pelvic splanchnic nerves. They synape in terminal ganglia associated with the rectum and genitourinary organs.

ADRENERGIC FUNCTION :

Adrenergic neurons influence and adjust body functions and their effects on circulation and respiration are among the important. The endogenous catecholamine norepinephrine and epinephrine possess alpha and beta receptor agonist activity.

Alpha 1receptor –Blood vessels (Arteries), Uterus,Vas deferens, Eye iris radial muscle, Urinary bladder (trigone and sphincter) Ureter Liver glycogenolysis and Nasal and salivary glands.

Alpha 2 receptor– Blood vessel (veins), GIT, Insulin release from pancreas.

Beta 1 receptor –Heart , kidney, fat cells.

Beta 2 receptor –Blood vessels (skeletal muscle), Bronchial tree, Eye (ciliary muscle), Urinary bladder (Detrusor).

CHOLINERGIC FUNCTION:

Release of Ach is the hallmark of parasympathetic activation. The actions of Ach are almost opposed to those of ne and epinephrine .

Ach effects,

1 . Decreases the HR.

2 . Decreases the velocity of conduction in the SA and AV nodes.

3 . Decreases Atrial contractility.

4 . Smooth muscle constriction (bronchial walls)

5.GIT and GENITOURINARY smooth muscle constricts

6.Sphinter muscles relax

Endothelial cells in blood vessels have receptors including serotonin, adenosine, histamine and catecholamines

Alpha 1 Agonist smooth muscle constriction eg,phenylephrine.

Alpha 2 Agonist presynaptic inhibits Norepinephrine release,

eg clonidine ,Dexmedetomidine,

Beta 1Agonist heart inotropy and chronotropy eg Dobutamine,

Beta 2Agonist smooth muscle dilation and relaxation eg Terbutaline .

ADRENERGIC PHARMACOLOGY:

Synthesis of Norepinephrine:

Synthetised from tyrosine by tyrosine hydroxylase actively transported into postganglionic sympathetic nerve ending. Tyrosine is derived from phenylalanine, they are taken up in large amounts in shock to maintain perfusion pressure. Chronic stress can elevate tyrosine hydroxylase levels by stimulating the synthesis of this enzyme. Approximately 85% of the Noradrenaline to epinephrine. Glucocorticoids from the adrenal cortex pass through the adrenal medulla and can activate the system and stress –induced steroid release can increase the production of epinephrine.

Storage of Norepinephrine:

Stored with in large, dence–core vesicles along with binding proteins, calcium, ATP.In general, 1% of the stored Norepinephrine is released with each depolarization,a significant reserve.

Release of Norepinephrine :

Exocytosis is the main dominant physiologic mechanism of release. Angiotensin II, Prostacycline and Histamine potentiate release, Acetylcholine and Prostaglandin E inhibit release.

Inactivation : Rapidly removed from the synaptic cleft by amine mechanism.or by nonneuronal tissue.The highest rate of reuptake is found in the heart ,having more effect on blood pressure.

Metabolism:

Asmall amount of the norepinephrine escapes uptake into the nervevending and enters the circulation, where it is metabolished by MAO ,COMT or both in the blood, liver and kidney.

ALPHA RECEPTOR AGONISTS:

Phenylephrine and methoxamine –alpha 1 agonists,commonly used when peripheral vasoconstriction is needed and cardiac output is adequate. Phenyl ephrine has a rapid onset and short duration of action, when given IV. It is applied topically ,alone or mixed with anesthetic gel ,to prepare the nostris for Nasotracheal intubation**.**

Alpha 2 Agonists are important adjuvants and analgesics,primary effect being sympatholytic.

1. To reduce peripheral norepinephrine release by stimulation of prejuctional inhibitory ALPHA2 receptor.
2. To inhibit central neural transmission in the dorsal horn by presynaptic and postsynaptic mechanism.

3. Direct sympatholytic effects on spinal preganglionic sympathetic neurons.

4. To have sedative,anxiolytic,and analgesic properties.

Clonidine and Dexmedetomidine – Alpha 2 Agonist.

Although Dexmedetomidine infusions attenuate the hemodynamic lability of induction, maintanence and emergence, the dose of other anesthetics must be carefully reduced. The dexmedetomidine is the rousable sedation, patients awaken from apparently deep status of sedation to verbal commands.

EXTUBATION OF THE TRACHEA:

A critical part of airway management is the process of extubation. A number of complications can develop during extubation, some are minor, others can lead to a failed extubation.

FAILED EXTUBATION;

1. Failure of oxygenation,
2. Failure of ventilation,
3. Inadequate clearance of pulmanory secretions,
4. Loss of Airway patency.

GENERAL CONSIDERATION S FOR EXTUBATION:

1. Plan for reintubation to maintain an adequate Airway patency ,
2. Plan for weather to extubate patient is fully awake or a deep extubation or bailey maneuver, exchanging an ETT for an SGA while the patient is under deep anesthesia.
3. To ensure adequate reversal or recovery from neuromuscular blockade, hemodynamic stability, normothermia, adequate analgesia.
4. Preoxygenated with a 100% inspired O2 and Alveolar recruitment maneuver .
5. Suctioning of the pharynx and trachea, removal of throat pack and the placement of a bite block,
6. NG tube should be suctioned, before extubation.
7. Sniffing position –standard position for extubation, optimally positioned for Airway management, if necessary
8. Application of positive pressure before cuff deflation may help clear the secretions,
9. To Inspect pilot balloon to ensure complete deflation before extubation.

COMPLICATIONS WITH EXTUBATION:

Laryngospasm and broncospasm

Upper Airway obstruction

Hypoventilation

Hemodynamic changes (HT, TACHYCARDIA)

Coughing and straining- surgical dehiscence

Laryngeal or Airway edema

Negative pressure pulmonary edema

Paradoxical vocal cord motion

Arytenoid dislocation

Aspiration.

FACTORS ASSOCIATED WITH INCREASED EXTUBATION RISK:

AIRWAY RISK FACTORS:

1) Known difficult airway
2) Airway deterioration (Bleeding , edema, trauma)
3) Restricted airway access
4) Obesity & Obstructive sleep apnea
5) Aspiration risk

GENERAL RISK FACTORS

1) Cardiovascular diseases
2) Respiratory disease
3) Neuromuscular disease
4) Metabolic derangements
5) Special surgical requirements

FIVE SIGNS OF RECOVERY FROM GENERAL ANESTHESIA

1) Patient must be fully awake & fully oriented
2) Patient should not suffer severe pain
3) Protective reflexes must have recovered fully & must be active enough to protect the airway
4) The residual NMB must have been fully reversed
5) The clinical sign of complete recovery of NMB must be there

FIVE SIGNS OF RECOVERY FROM MUSCLE RELAXANTS EFFECTS

1) Ability to open eyes & sustained it for more than 5 seconds
2) Ability to protrude the tongue out of oral cavity , the tip must be sharp

3) Ability to close the mouth & swallow
4) Ability to lift the hand & touching the nose and going back to its original position with full co-ordination
5) Ability to lift the head away from the pillow and sustained it for more than 5 seconds.

HISTORICAL BACKGROUND

In 1847, John snow described ether anaesthesia in five stages. This was redefined by Guedel into four stages based upon respiration, muscle tone and ocular signs. Guedel's stage I of anaesthesia in 1954 was divided by Artusio into 3 planes.

Arthur Ernest Guedel in 1937 described the anaesthetic state based on diethyl ether, inhalational agent. It is based on respiratory parameters, size of pupils, eyelash reflex, eyeball movements and muscle movements.

Endotracheal intubation for anaesthesia was popularised by Ivan Magill and Stanley Rowbotham. They developed the apparatus used for "insufflation anaesthesia" where gases were blown into the trachea through a narrow tube, and allowed to spill out through the otherwise open airway.

This technique proved unsatisfactory for anaesthetising patients undergoing plastic surgery to the head and neck, victims of injuries from the 1914-18 war. A wider tube allowing to and fro motion of the gases was better. It was Harold Griffith who later introduced curare into clinical practice in 1942 and recognised the value of endotracheal

intubation, not for head and neck procedures, but to provide good operating conditions during abdominal surgery. Without relaxants, he and others such as Guedel were rendering patients apnoeic and “relaxed” with cyclopropane, and manually providing positive pressure ventilation.

DEXMEDETOMIDINE

Dexmedetomidine is a new generation highly selective α2-adrenergic receptor (α2-AR) agonist that is associated with sedative and analgesic sparing effects, reduced delirium and agitation, perioperative sympatholysis, cardiovascular stabilizing effects, and preservation of respiratory function. The aim of this review is to present the most recent topics regarding the advantages in using dexmedetomidine in clinical anesthesia and intensive care, while discussing the controversial issues of its harmful effects.

α2-adrenergic receptor (α2-AR) agonists have been successfully used in several clinical settings in view of diverse actions which include sedation, analgesia, anxiolysis, perioperative sympatholysis, cardiovascular stabilizing effects, reduced anesthetic requirements, and preservation of respiratory function. Dexmedetomidine is a relatively new drug approved at the end of 1999 by the Food and Drug Administration (FDA) for humans use for short-term sedation and analgesia (<24 hours) in the intensive care unit (ICU). Dexmedetomidine is a useful sedative agent with analgesic properties, hemodynamic stability and ability to recover respiratory function in

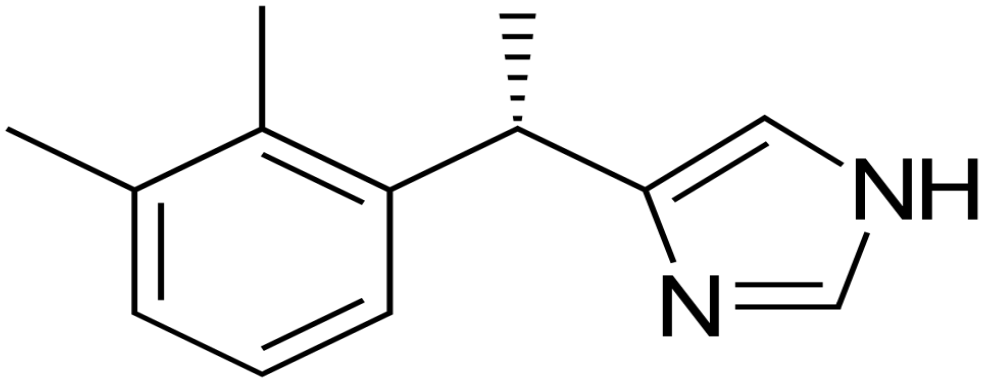
mechanically ventilated patients facilitating early weaning. Besides being a new modality of sedation and analgesia in ICU patient management, it has been studied in several other perioperative settings, which will be discussed.

History

Dexmedetomidine was approved in 1999 by the US Food and Drug Administration (FDA) as a short-term sedative and analgesic (<24 hours) for critically ill or injured people on mechanical ventilation in the intensive care unit (ICU). The rationale for its short-term use was due to concerns over withdrawal side effects such as rebound high blood pressure. These effects have not been consistently observed in research studies, however. In 2008 the FDA expanded its indication to include non-intubated people requiring sedation for surgical or non-surgical procedures, such as colonoscopy.

CHEMICAL STRUCTURE

Dexmedetomidine is the dextrorotatory S-enantiomer of medetomidine, an agent used in veterinary medicine. It is chemically (S)-4-[1-(2,3-dimethylphenyl) ethyl]-3H-imidazole



Chemical structure of dexmedetomidine

MECHANISM OF ACTION

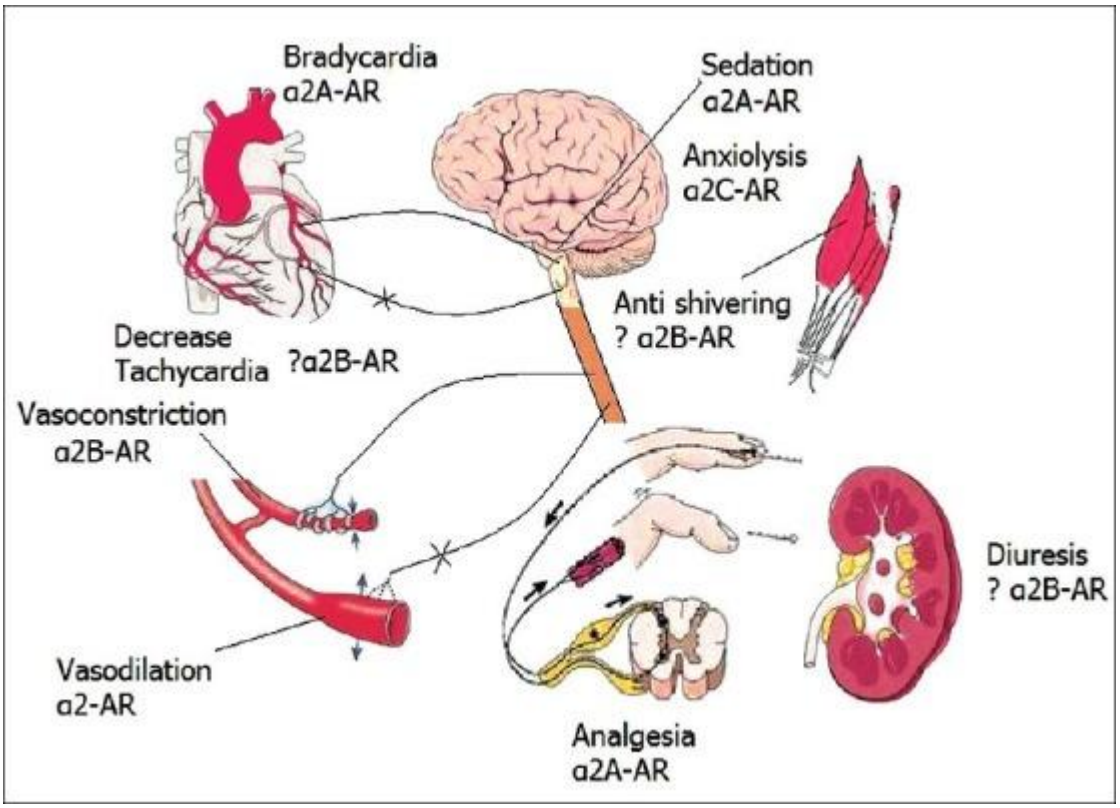
α2-AR agonists produce clinical effects after binding to G-Protein-coupled α2-AR, of which there are three subtypes (α2A, α2B, and α2C) with each having different physiological functions and pharmacological activities. These receptor subtypes are found ubiquitously in the central, peripheral, and autonomic nervous systems, as well as in vital organs and blood vessels. Dexmedetomidine is 8 to 10 times more selective towards α2-AR than clonidine. Neither clonidine nor dexmedetomidine is totally selective for any one of the

α2-AR subtypes, but dexmedetomidine seems to have higher α2A-AR and α2C-AR affinity than clonidine. Major differences in the pharmacology of clonidine and dexmedetomidine have been described below. Comparison of clonidine with dexmedetomidine

Clonidine	Dexmedetomidine
Developed in the 1960s	Developed in the 1980s
Clinically used first as antihypertensive in 1966	Clinically approved as sedative and analgesic used in ICU in 1999
Ratio α 2:α 1 receptor binding is 220:1	Dexmedetomidine is 7-8 times more specific for a2. Ratio α 2:α 1 receptor binding is 1620:1
Clonidine is a partial agonist at the α 2 adrenergic receptor	Dexmedetomidine is a full agonist at the α 2 adrenergic receptor
Octanol/buffer partition coefficient: 0.8	Octanol/buffer partition coefficient: 2.8 more lipophilic (3.5-fold) than clonidine
The maximum reduction in inhalational anesthetic requirement to maintain 1 MAC provided by clonidine is 50%	Dexmedetomidine has been shown to result in approximately a 90% reduction in inhalational anesthetic requirement to maintain 1 MAC
Plasma half-life is T½: 9-12 hours	Plasma half-life T½: 2-2.5 hours
Protein binding: 50%	Protein binding: 94%
Elimination half life is 8 hrs	Elimination half life is 2 hrs
Distribution half life is >10 min	Distribution half life is 5 min

Locus ceruleus of the brain stem is the principal site for the sedative action and spinal cord is the principal site for the analgesic action, both acting through α2A-AR. In the heart, the dominant action

of α2-AR agonists is a decrease in tachycardia (through blocking cardioaccelerator nerve) and bradycardia via α2A-AR (through a vagomimetic action). In the peripheral vasculature, there is sympatholysis-mediated vasodilatation and smooth muscle cells receptor-mediated vasoconstriction. The mechanism for the antishivering and diuretic actions has yet to be established firmly.



Physiology of various α2-adrenergic receptors

The responses to activation of the receptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas. Combining all these effects, dexmedetomidine avoids some of the side effects of multiagent therapies.

PHARMACOKINETICS

Absorption and distribution

Dexmedetomidine exhibits linear pharmacokinetics in the recommended dose range of 0.2 to 0.7 μg/ kg/ hr administered as intravenous infusion up to 24 hours. The distribution phase is rapid, with a half-life of distribution of approximately 6 minutes and elimination half life of 2 hours. The steady-state volume of distribution is 118 L. The average protein binding is 94% and is constant across the different plasma concentrations and also similar in males and females. It has negligible protein binding displacement by

drugs commonly used during anesthesia and in the ICU like fentanyl, ketorolac, theophylline, digoxin, and lidocaine. Context-sensitive half life ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion. Oral bioavailability is poor because of extensive first-pass metabolism. However, bioavailability of sublingually administered dexmedetomidine is high (84%), offering a potential role in pediatric sedation and premedication.

Metabolism and excretion

Dexmedetomidine undergoes almost complete biotransformation through direct N-glucuronidation and cytochrome P-450 (CYP 2A6)-mediated aliphatic hydroxylation to inactive metabolites. Metabolites are excreted in the urine (about 95%) and in the feces (4%). Dose adjustments are required in patients with hepatic failure because of lower rate of metabolism.

CLINICAL PHARMACOLOGY

Cardiovascular system

Dexmedetomidine evokes a biphasic blood pressure response: A short hypertensive phase and subsequent hypotension. The two phases are considered to be mediated by two different α2-AR subtypes: the α-2B AR is responsible for the initial hypertensive phase, whereas hypotension is mediated by the α2A-AR. In younger patients with high levels of vagal tone, bradycardia and sinus arrest have been described which were effectively treated with anticholinergic agents (atropine, glycopyrrolate).

Central nervous system

Dexmedetomidine reduces cerebral blood flow and cerebral metabolic requirement of oxygen but its effect on intracranial pressure (ICP) is not yet clear. Dexmedetomidine modulates spatial working memory, enhancing cognitive performance besides having sedative, analgesic, and anxiolytic action through the α2-AR. Studies suggest the likelihood of its neuroprotective action by reducing the levels of circulating and brain catecholamines and thus balancing the ratio between cerebral oxygen supplies, reducing excitotoxicity, and

improving the perfusion in the ischemic penumbra. It reduces the levels of the glutamate responsible for cellular brain injury, especially in subarachnoid hemorrhage. It has been shown to limit the morphologic and functional effects after ischemic (focal and global) and traumatic injury to the nervous system.

Respiratory effects

Dexmedetomidine affect on respiration appears to be similar in order of magnitude to those seen in the heavy sleep state. Dexmedetomidine does not suppress respiratory function, even at high doses. It has no adverse effects on respiratory rate and gas exchange when used in spontaneously breathing ICU patients after surgery. It helps in maintaining sedation without cardiovascular instability or respiratory drive depression and hence may facilitate weaning and extubation in trauma/surgical ICU patients who have failed previous attempts at weaning because of agitation and hyperdynamic cardiopulmonary response.

Endocrine and renal effects

Dexmedetomidine activates peripheral presynaptic α2- AR which reduces the release of catecholamines, and hence reduces

sympathetic response to surgery. Animal studies have demonstrated the occurrence of natriuresis and diuresis. Dexmedetomidine is an imidazole agent but unlike etomidate, it does not appear to inhibit steroidogenesis when used as an infusion for short-term sedation.

ADVERSE EFFECTS

The various reported side effects are hypotension, hypertension, nausea, vomiting, dry mouth, bradycardia, atrial fibrillation, pyrexia, chills, pleural effusion, atelectasis, pulmonary edema, hyperglycemia, hypocalcaemia, acidosis, etc. Rapid administration of dexmedetomidine infusion (Loading dose of 1 μ/ kg/ hr if given in less than 10 minutes) may cause transient hypertension mediated by peripheral α2B- AR vasoconstriction. But hypotension and bradycardia may occur with ongoing therapy mediated by central α2A-AR, causing decreased release of noradrenaline from the sympathetic nervous system. Long-term use of dexmedetomidine leads to super sensitization and upregulation of receptors; so, with abrupt discontinuation, a withdrawal syndrome of nervousness, agitation, headaches, and hypertensive crisis can occur. Dexmedetomidine is not recommended in patients with advanced

heart block and ventricular dysfunction. FDA has classified it as a category C pregnancy risk, so the drug should be used with extreme caution in women who are pregnant.

CLINICAL APPLICATIONS OF DEXMEDETOMIDINE

Premedication

Dexmedetomidine is used as an adjuvant for premedication, especially in patients susceptible to preoperative and perioperative stress because of its sedative, anxiolytic, analgesic, sympatholytic, and stable hemodynamic profile. Dexmedetomidine decreases oxygen consumption in intraoperative period (up to 8%) and in postoperative period (up to 17%). Premedication dose is 0.33 to 0.67 mg/kg IV given 15 minutes before surgery (this dose minimizes side effects of hypotension and bradycardia).

Intraoperative use

Dexmedetomidine attenuates hemodynamic stress response to intubation and extubation by sympatholysis. In view of absent respiratory depression, it can be continued at extubation period unlike other drugs. Dexmedetomidine potentiates anesthetic effect of all the anesthetic agents irrespective of the mode of administration

(intravenous, inhalation, regional block). Intraoperative administration of dexmedetomidine in lower concentrations has reduced the requirement of other anesthetic agents; fewer interventions to treat tachycardia; and a reduction in the incidence of myocardial ischemia. However, side effects like bradycardia and hypotension are limitations to its use necessitating need for pharmacological rescue therapy. These effects may be attributed to the combined properties of volatile anesthetics such as vasodilatation and myocardial depression. Dexmedetomidine administered in high concentrations may cause systemic and pulmonary hypertension because of direct peripheral vascular effects or may compromise myocardial function and blood pressure.

Regional analgesia

Highly lipophilic nature of dexmedetomidine allows rapid absorption into the cerebrospinal fluid and binding to α2-AR of spinal cord for its analgesic action. It prolongs the duration of both sensory and motor blockade induced by local anesthetics irrespective of the route of administration (e.g., epidural, caudal, or spinal). Dexmedetomidine though enhances both central and peripheral neural

blockade by local anesthetics; however, the peripheral neural blockade is due to its binding to α2A-AR. Dexmedetomidine has been successfully used in intravenous regional anesthesia (IVRA), brachial plexus block, and intraarticularly. Addition of 0.5 μg/kg dexmedetomidine to lidocaine for IVRA improves quality of anesthesia and improves intraoperative-postoperative analgesia without causing side effects. Dexmedetomidine added to levobupivacaine for axillary brachial plexus block shortens the onset time and prolongs the duration of the block and postoperative analgesia. Intraarticular dexmedetomidine in patients undergoing arthroscopic knee surgery improves the quality and duration of postoperative analgesia.

Sedation in intensive care unit

Dexmedetomidine has become popular sedative agent in ICU because of its ability to produce cooperative sedation, i.e., patients remain awake, calm, and are able to communicate their needs. It does not interfere with the respiratory drive or produce any agitation, hence facilitating early weaning from ventilator, thereby reducing overall ICU stay costs. The maintenance of natural sleep during sedation

might speed recovery time in the ICU. Dexmedetomidine currently is approved by FDA for use in ICU for not more than 24 hours; though many studies have reported its safe use for longer duration. Dexmedetomidine, when compared with conventional sedatives and opiates, has been demonstrated to be associated with both sedative and analgesic sparing effects, reduced delirium and agitation, minimal respiratory depression, and desirable cardiovascular effects.

Dexmedetomidine is an attractive agent for short-term procedural sedation and has been safely used in transesophageal echocardiography, colonoscopy, awake carotid endarterectomy, shockwave lithotripsy, vitreoretinal surgery, elective awake fiberoptic intubation, pediatric patients undergoing tonsillectomy, and pediatric MRI. The usual dose of dexmedetomidine for procedural sedation is 1 μg/ kg, followed by an infusion of 0.2 μg/kg/h. Its onset of action is less than 5 minutes and the peak effect occur within 15 minutes. As the pharmacologic effects of dexmedetomidine can be reversed by the α2-AR antagonist atipamezole, dexmedetomidine provides a titratable form of hypnotic sedation that can be readily reversed.

Controlled hypotension

Dexmedetomidine is an effective and safe agent for controlled hypotension mediated by its central and peripheral sympatholytic action. Its easy administration, predictability with anesthetic agents, and lack of toxic side effect while maintaining adequate perfusion of the vital organs makes it a near-ideal hypotensive agent. Spinal fusion surgery for idiopathic scoliosis, septoplasty and tympanoplasty operations, and maxillofacial surgery have been safely done with dexmedetomidine-controlled hypotension.

Analgesia

Dexmedetomidine activates α2-AR in the spinal cord reducing transmission of nociceptive signals like substance P. It has significant opioid sparing effect and is useful in intractable neuropathic pain.

Cardiac surgery

Dexmedetomidine in addition to blunting the hemodynamic response to endotracheal intubation also reduces the extent of myocardial ischemia during cardiac surgery. Dexmedetomidine has been successfully used to manage patients with pulmonary hypertension undergoing mitral valve replacement, with reduction in

pulmonary vascular resistance, pulmonary artery pressure, and pulmonary capillary wedge pressures.

Neurosurgery

Dexmedetomidine provides stable cerebral hemodynamics without sudden increase in ICP during intubation, extubation, and head pin insertion. It attenuates neurocognitive impairment (delirium and agitation) allowing immediate postoperative neurological evaluation. It exerts its neuroprotective effects through several mechanisms which make the usage of this drug a promising tool during cerebral ischemia. It does not interfere with neurological monitors and has an upcoming role in “functional” neurosurgery. This includes awake craniotomy for the resection of tumors or epileptic foci in eloquent areas, and the implantation of deep brain stimulators for Parkinson's disease. Dexmedetomidine is notable for its ability to provide sedation without risk of respiratory depression (unlike other commonly used drugs such as propofol and fentanyl) and can provide cooperative or semi-rousable sedation. Similar to clonidine, it is an agonist of α_2-adrenergic receptors in certain parts of the brain. Dexmedetomidine hydrochloride is also used in veterinary medicine for dogs and cats.

Dosage and administration

Intravenous infusion of dexmedetomidine is commonly initiated with a loading dose followed by a maintenance infusion. There may be great individual variability in the hemodynamic effects (especially on heart rate and blood pressure), as well as the sedative effects of this drug. For this reason, the dose must be carefully adjusted to achieve the desired clinical effect.

Side effects

There is no absolute contraindication to the use of dexmedetomidine. It has a biphasic effect on blood pressure with lower readings at lower drug concentrations and higher readings at higher concentrations. Rapid IV administration or bolus has been associated with hypertension due to peripheral α_2-receptor stimulation. Bradycardia can be limiting factor with infusions especially in higher doses.

Interactions

Dexmedetomidine may enhance the effects of other sedatives and anesthetics when co-administered. Similarly, drugs that lower blood pressure and heart rate, such as beta blockers, may also have enhanced effects when co-administered with dexmedetomidine.

Pharmacology

Pharmacodynamics

Dexmedetomidine is a highly selective α_2-adrenergic agonist. Unlike opioids and other sedatives such as propofol, dexmedetomidine is able to achieve its effects without causing respiratory depression. Dexmedetomidine induces sedation by decreasing activity of noradrenergic neurons in the locus ceruleus in the brain stem, thereby increasing the activity of inhibitory gamma-aminobutyric acid (GABA) neurons in the ventrolateral preoptic nucleus. other sedatives like propofol and benzodiazepines directly increase activity of gamma-aminobutyric acid neurons.

Sedation by dexmedetomidine mirrors natural sleep. As such, dexmedetomidine provides less amnesia than benzodiazepines. Dexmedetomidine also has analgesic effects at the spinal cord level and other supraspinal sites.[19] Thus, unlike other hypnotic agents like propofol, dexmedetomidine can be used as an adjunct medication to help decrease the opioid requirements of people in pain while still providing similar analgesia.

REVIEW OF LITERATURE

Effects of Dexmedetomidine on Intraoperative Hemodynamics and Propofol Requirement in Patients Undergoing Laparoscopic Cholecystectomy. Avneesh Khare, Satya Prakash Sharma,[1] Mangi Lal Deganwa,[2] Mamta Sharma,[3] and Nitesh Gill[4] Anesth Essays Res. 2017 Oct-Dec; 11(4)

Background: Despite multiple benefits, laparoscopic surgery always poses anesthetic challenge due to significant alteration of hemodynamics. Various pharmacological agents have been used for the same with variable response. Dexmedetomidine, in addition to sympatholytic effect, diminishes intraoperative requirement of anesthetics including propofol. The present study was conducted to evaluate the effects of intravenous dexmedetomidine on intraoperative hemodynamics and propofol requirement using bispectral index (BIS) in laparoscopic cholecystectomy.

Results: After intubation, MAP and HR values in Group A were significantly lower than Group B at various time points of study. To achieve similar BIS values, significantly low doses of propofol were required in Group A during induction and intraoperatively. Doses

were reduced by 36% and 31%, respectively. Mean recovery time and mean extubation time in Group A were also significantly less.

Conclusion: During propofol-based anesthesia for laparoscopic cholecystectomy, dexmedetomidine provides stable intraoperative hemodynamics and reduces propofol requirement for induction as well as maintenance, without compromising recovery profile.

The effectiveness of intravenous dexmedetomidine on perioperative hemodynamics, analgesic requirement, and side effects profile in patients undergoing laparoscopic surgery under general anesthesia**Year : 2017 | Volume : 11 | Issue : 1 | Page : 72-77**

Vinayak Panchgar[1], Akshaya N Shetti[2], HB Sunitha[3], Vithal K Dhulkhed[4], AV Nadkarni[4]

Aims and Objectives: (a) To study the effect of dexmedetomidine on hemodynamic parameters during perioperative period in patients undergoing laparoscopic surgery. (b) To study the postoperative sedation score and analgesic requirement. (c) To study the side effect profile of dexmedetomidine. Settings and Design: Randomized double blind controlled trial.. Results: Significant hemodynamic changes are observed in NS group during laryngoscopy, intubation, during pneumoperitoneum formation, and during extubation. Hemodynamic stress response in dexmedetomidine group was significantly attenuated. Analgesic requirement during postoperative 24 h were much less in dexmedetomidine group when compared to NS group. No significant side effects were noted except for bradycardia; which was observed in two cases of dexmedetomidine group. Conclusion: Dexmedetomidine

infusion in the dose of 1 μg/kg body weight as bolus over 10 min and 0.5 μg/kg/h intraoperatively as maintenance dose controlled the hemodynamic stress response in patients undergoing laparoscopic surgery. Use of dexmedetomidine extends the pain free period postoperatively and thereby reducing total analgesic requirement. Thus, dexmedetomidine can be utilized as an ideal anesthetic adjuvant during laparoscopic surgeries.

EFFECT OF DEXMEDETOMIDINE ON HEMODYNAMIC PARAMETERS DURING EXTUBATION. A PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY : Shruthi AH*, Nethra SS, Sudheesh K***, Devika Rani D and Raghavendra Rao RS**

Middle East J Anaesthesiol. 2016 Feb;23(4):457-63

Extubation is known to produce significant hemodynamic disturbances. There is a need to avoid increase in heart rate and blood pressure in hypertensive and cardiac patients and in vascular, neuro and intraocular surgeries. Aim to study the ability of dexmedetomidine to attenuate the hemodynamic responses during extubation.

Materials and methods: 80 patients of ASA Grade I-II aged 18-50 years received standard anesthesia. At the closure of skin incision, patients were randomly allocated to receive either dexmedetomidine 0.5 μg/kg (Group D) or saline placebo (Group C) intravenously over 10 minutes in a double-blind design. Heart rate (HR), systolic, diastolic and mean arterial pressures (SBP, DBP, MAP) were assessed before, during and after extubation. Time to eye opening and extubation, sedation, complications such as coughing, laryngospasm, bronchospasm and desaturation were recorded.

Results: HR, SBP, DBP and MAP were comparable to basal values in group D at extubation and lower than baseline values post-extubation but significant increase was noted in group C (P<0.001). Time to extubation and eye opening were prolonged in Group D (P <0.001). Incidence of hypotension was more in group D (22%) but was transient. Incidence of coughing was lower in Group D than in group C (P <0.001). Patients in group D were more sedated for 30 minutes post extubation.

Conclusion: Dexmedetomidine 0.5 μg/kg given before extubation attenuates hemodynamic reflexes during emergence from anesthesia without causing undue sedation, but prolongs time to extubation.

Effects of low dose dexmedetomidine infusion on haemodynamic stress response, sedation and post-operative analgesia requirement in patients undergoing laparoscopic cholecystectomy Year : 2014 | Volume : 58 | Issue : 6 | Page : 726-731

Gourishankar Reddy Manne, Mahendra R Upadhyay, VN Swadia
Department of Anaesthesiology, Medical College, Vadodara, Gujarat, India

Background and Aim: Dexmedetomidine is a α2 agonist with sedative, sympatholytic and analgesic properties and hence, it can be a very useful adjuvant in anaesthesia as stress response buster, sedative and analgesic. We aimed primarily to evaluate the effects of low dose dexmedetomidine infusion on haemodynamic response to critical incidences such as laryngoscopy, endotracheal intubation, creation of pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. The secondary aims were to observe the effects on extubation time, sedation levels, post-operative analgesia requirements and occurrence of adverse effects. Results: In Group NS significant haemodynamic stress response was seen following laryngoscopy, tracheal intubation, creation of pneumoperitoneum and extubation. In dexmedetomidine groups, the

haemodynamic response was significantly attenuated. The results, however, were statistically better in Dex 0.4 group compared with Dex 0.2 group. Post-operative 24 hour analgesic requirements were much less in dexmedetomidine groups. No significant side effects were noted. Conclusion: Low dose dexmedetomidine infusion in the dose of 0.4 mcg/kg/h effectively attenuates haemodynamic stress response during laparoscopic surgery with reduction in post-operative analgesic requirements.

ATTENUATION OF HEMODYNAMIC STRESS RESPONSE DURING EMERGENCE FROM GENERAL ANAESTHESIA: A PROSPECTIVE RANDOMIZED CONTROLLED STUDY COMPARING FENTANYL AND DEXMEDETOMIDINE

Liyakhath Ali1, Siddhram Jamgond2, Jagadish M. **November year 2014 Volume : 3 Issue : 62 Page : 13686-13696**

BACKGROUND: Tracheal extubation and emergence is associated with significant haemodynamic alterations and is poorly tolerated by patients with co-morbid conditions. We compared the efficacy of fentanyl and dexmedetomidine in mitigating haemodynamic stress response and assessed extubation quality in study groups.. RESULTS: All the measured haemodynamic parameters were significantly elevated at extubation and at various points of observation in normal saline group than fentanyl and dexmedetomidine group (p=0.000). Tachycardia response was seen in 84% patients in group N, compared to 36% and 8% in group F & D respectively (p=0.000). Statistically significant hypertensive response was noticed in 43(86%) patients of group N, 9(18%) of group F and 3(6%) of group D (p=0.000). Duration of tachycardia and hypertensive response was significantly longer in control group. Three groups differed with regard to overall

extubation quality ($p<0.001$). Groups D (1.50±0.58) and F (1.94±0.55) had lower scores compared to group N (2.68±0.47) implying smoother extubation. Use of rescue drugs to treat acute hypertensive response was more in group N (34%) than group F (2%) and group D (0%). Sedation and recovery scores were similar in all the three groups. CONCLUSION: Dexmedetomidine 1 µg/kg IV was most effective followed by fentanyl 1 µg/kg IV in attenuating haemodynamic stress responses during emergence with no clinically significant differences in sedation and recovery profile. Dexmedetomidine group had smoother and best extubation quality.

AIM OF THE STUDY

The primary objective was to assess the effects of Dexmedetomidine when given at a dose of 0.5 microgram/Kg just before extubation on hemodynamic responses to emergence from anesthesia.

The secondary objective was the effects on recovery.

MATERIALS AND METHODOLOGY

After obtaining hospital ethical committee approval and the informed written consent obtained from the patients participating in the study, a randomised double blind study was performed. By considering the statistical power of 95% and type one error of $\alpha = 5\%$, 80 patients were selected and divided into two group of control group and group-Dexmeditomidine with 40 patients in each group, belonging to ASA I & II posted for elective abdominal surgeries. They were randomly allocated to 40 patients of control group and 40 patients of Dexmeditodine group.

After shifting patient to the operating room ,intravenous access was obtained and Ringer lactate solution started. All patients were monitored with ECG, Pulse oximetry ,Non invasive BP, ETCO2,and basal parameters were recorded. General Anesthesia was given in usual way. At the beginning of closure of skin incision inhalational anesthetic agent was turned off and the muscle relaxant stopped.

Study Group : (n=40)patients received 0.5microgram/Kg Dexmedetomidine diluted in 10ml normal saline

Control Group : (n=40)patients received 10ml of normal saline (placebo).

Heart rate, Systolic Blood pressure , Diastolic Blood pressure, Mean arterial pressure, Percentage saturation of oxygen were recorded preoperatively, intraoperately, 1,5,7,10 min during infusion, following reversal administration and post extubation every 5 min for 15min , and then every 15min for next 2 hrs thereafter.

Statistical Analysis :

With the power of study being 80% and confidence limits at 95%, a minimum sample size required to detect 30% difference in heart rate between study and control groups was 24 patients in each group. We conducted study with 40 patients in each group to make it more authentic. Descriptive and inferential statistical analysis was carried out. Results on continuous measurements are presented on Mean + SD and results on categorical measurements are presented in Number (%). Student test (two tailed, independent) was used to test the significance of study parameters on continuous scale for intergroup and intragroup analysis on metric parameters. Levene's test for homogeneity of variance was performed to assess the homogeneity of variance. Chi-square / Fisher exact test was used to test the significance of study parameters on categorical scale between two

groups. Statistical software SPSS version 16 was used for the data analysis. p value <0.05 was considered statistically significant.

Inclusion criteria :

Age 18 to 60 years

ASA I and II

Abdominal surgery under general anesthesia

Exclusion criteria

ASA III & IV

Pulmonary disease and endocrine disorders

Head & Neck surgeries

Difficult airway

History of sleep apnoea

Ramsay sedation scale.

1.Anxious and agitated, restless.

2.Co-operative, oriented, tranquil.

3.Responsive to verbal commands ,drowsy.

4.Asleep, responsive to light stimulation.

5.Asleep, slow response to stimulation.

6.No response to stimulation.

RESULTS

TABLE – 1

AGE COMPARISON

AGE	CONTROL	STUDY
18 - 30	16	24
31 - 45	16	6
> 45	8	10
Total	40	40
Mean	35.625	34.925
SD	10.841	13.792
p value	0.801	Not sig

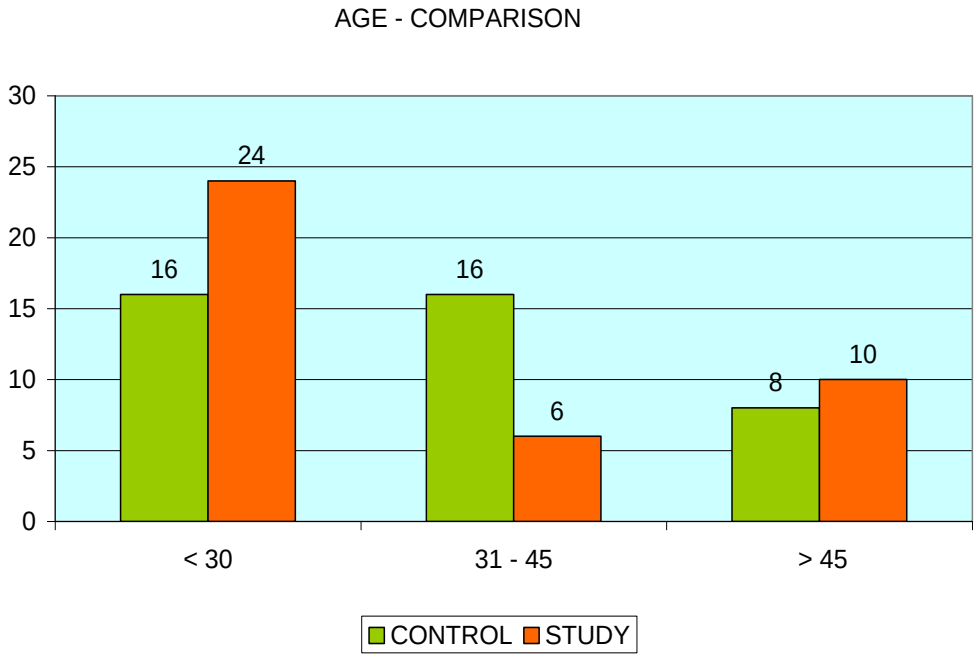


TABLE – 2

GENDER COMPARISON

Sex	CONTROL	STUDY
MALE	23	17
FEMALE	17	23
Total	40	40
p value	0.264	Not sig

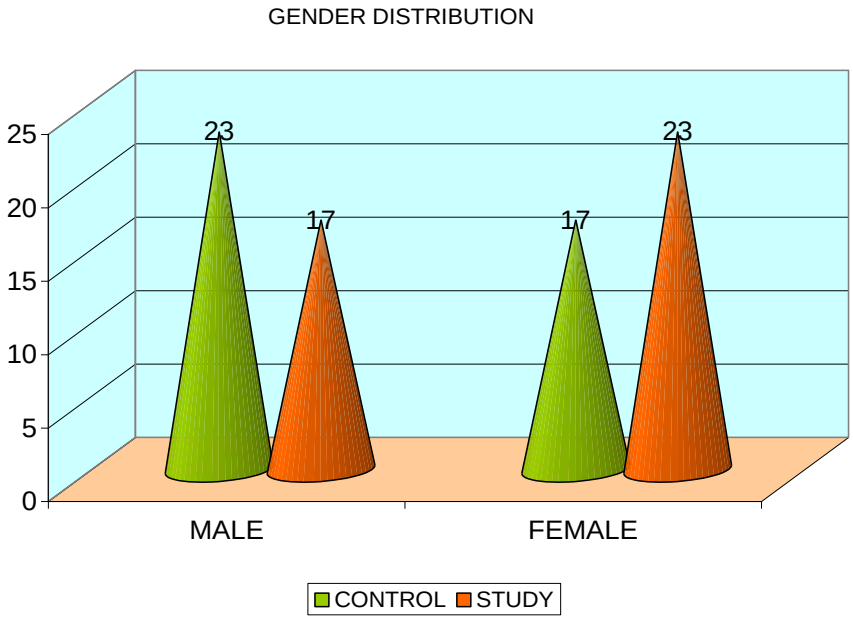


TABLE – 3

HEART RATE COMPARISON

HEART RATE	CONTROL GROUP		STUDY GROUP		p value	Significance
	MEAN	SD	MEAN	SD		
PREOP	85.225	7.777	89.35	8.79	0.029	Sig
INTRAOP	81.475	8.155	80.525	7.743	0.595	Not sig
During Infusion 1m	80.4	7.841	81.425	6.512	0.527	Not sig
5m	81.6	9.262	78.875	7.707	0.157	Not sig
7m	78.9	8.372	77.425	7.045	0.397	Not sig
10m	80.35	8.463	78.325	7.116	0.25	Not sig
RECOVERY	98	11.934	80.5	6.076	<0.001	Sig
Post extubation 5m	96.175	12.618	78.025	5.498	<0.001	Sig
10m	92.6	11.747	75.625	5.943	<0.001	Sig
15m	89.45	11.165	77	6.437	<0.001	Sig
30m	87.275	8.936	73.15	4.394	<0.001	Sig
45m	88.8	6.929	74	5.866	<0.001	Sig
60m	85.125	5.288	72.3	3.995	<0.001	Sig
75m	83.7	5.979	76.175	6.578	<0.001	Sig
90m	83.75	7.748	73.5	5.751	<0.001	Sig
105m	79.825	6.679	71.775	4.288	<0.001	Sig
120m	78.25	5.669	74.1	7.225	0.005	Sig

Inference : In study group, compare to control group there was significant decrease in heart rate with the p value of <0.001 during recovery and post extubation. But there was no significant changes in intra operative period .There was no tachycardia during recovery and post extubation time in the study (dexmedetomidine group).

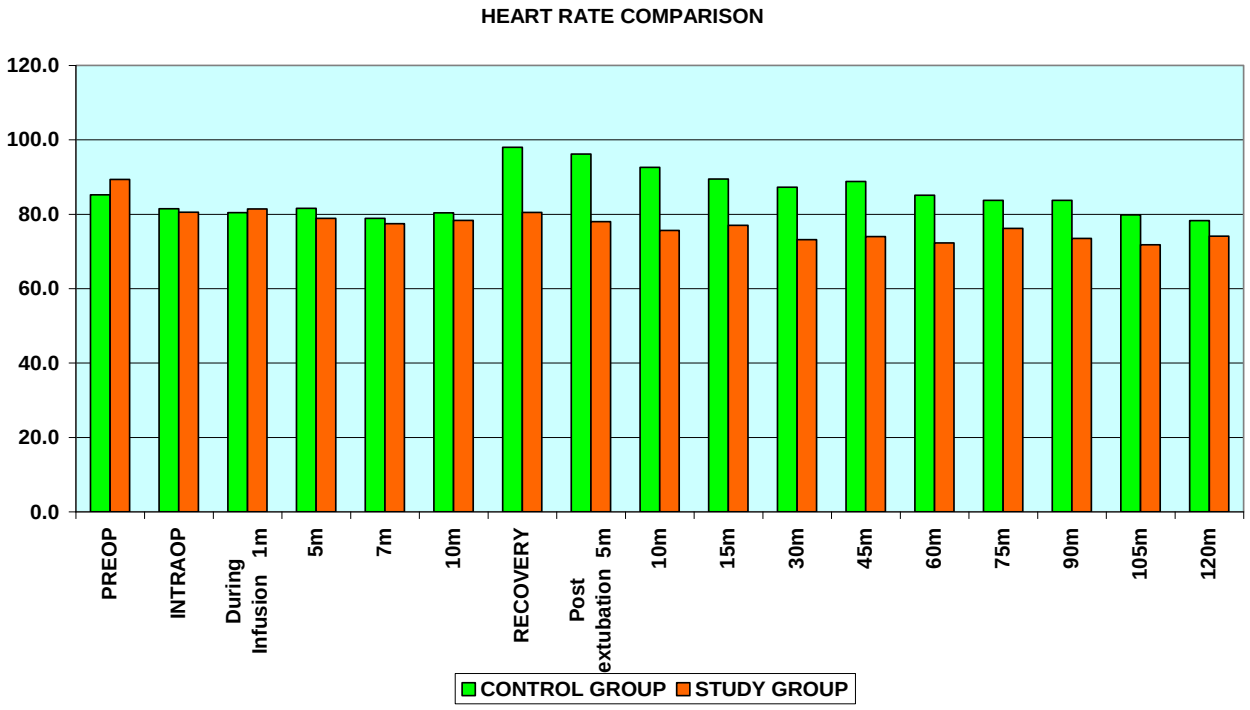

HEART RATE COMPARISON
120.0
100.0
80.0
60.0
40.0
20.0
0.0
PREOP
INTRAOP
During Infusion 1m
5m
7m
10m
RECOVERY
Post extubation 5m
10m
15m
30m
45m
60m
75m
90m
105m
120m
CONTROL GROUP
STUDY GROUP

TABLE – 4

SYSTOLIC BP

SBP	CONTROL GROUP		STUDY GROUP		p value	Significance
	MEAN	SD	MEAN	SD		
PREOP	129.48	10.92	125.65	12.38	0.147	Not sig
INTRAOP	117.58	10.62	117.50	13.91	0.978	Not sig
During Infusion 1m	125.35	7.99	115.13	10.24	<0.001	Sig
5m	123.65	7.78	114.18	8.82	<0.001	Sig
7m	120.95	7.09	109.98	8.31	<0.001	Sig
10m	118.93	7.38	110.85	11.71	<0.001	Sig
RECOVERY	138.25	13.41	117.05	8.86	<0.001	Sig
Post extubation 5m	134.40	8.23	112.50	8.17	<0.001	Sig
10m	127.85	7.54	114.35	10.75	<0.001	Sig
15m	126.15	6.78	111.10	6.75	<0.001	Sig
30m	123.45	6.86	107.73	6.38	<0.001	Sig
45m	121.65	6.08	112.70	10.03	<0.001	Sig
60m	121.30	7.39	109.50	6.33	<0.001	Sig
75m	117.40	4.94	107.58	6.14	<0.001	Sig
90m	119.18	8.28	106.53	5.40	<0.001	Sig
105m	118.00	6.37	109.58	6.36	<0.001	Sig
120m	115.55	6.45	109.10	6.08	<0.001	Sig

Inference :In study group ,when compared to control group there was a significant reduction(p-value of <0.001) in systolic blood pressure after infusion, during recovery and post extubation period and in control group there was elevation in all above periods.

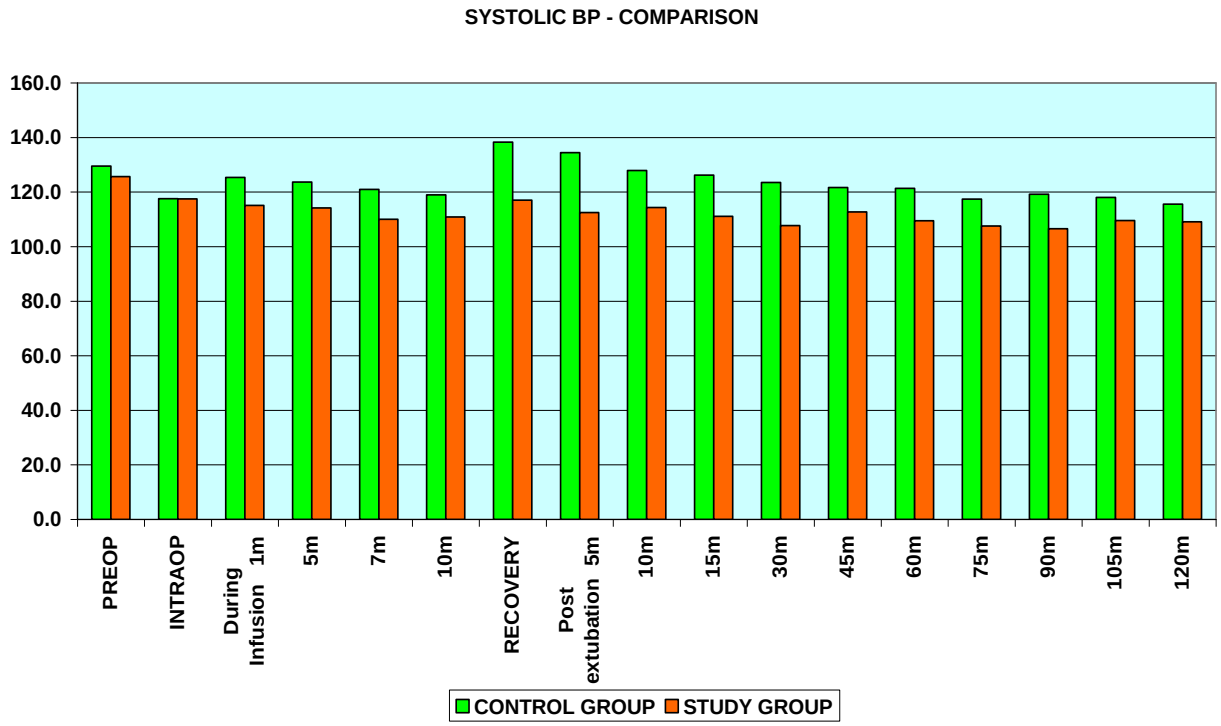

SYSTOLIC BP - COMPARISON
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
PREOP
INTRAOP
During Infusion 1m
5m
7m
10m
RECOVERY
Post extubation 5m
10m
15m
30m
45m
60m
75m
90m
105m
120m
CONTROL GROUP
STUDY GROUP

TABLE – 5

DIASTOLIC BP

DBP	CONTROL GROUP		STUDY GROUP		p value	Significance
	MEAN	SD	MEAN	SD		
PREOP	82.9	10.268	81.275	8.881	0.451	Not sig
INTRAOP	76.075	9.211	71.875	6.958	0.024	Sig
During Infusion 1m	80.85	5.968	72.475	5.444	<0.001	Sig
5m	80.725	6.872	73.625	7.544	<0.001	Sig
7m	78.875	6.649	69.05	5.013	<0.001	Sig
10m	78.05	5.883	68.775	5.704	<0.001	Sig
RECOVERY	83.5	7.158	78.5	5.174	<0.001	Sig
Post extubation 5m	88.425	5.406	73.95	3.935	<0.001	Sig
10m	86.4	5.007	71.575	4.84	<0.001	Sig
15m	86.275	4.438	73.575	6.496	<0.001	Sig
30m	83.55	6.824	68.825	3.079	<0.001	Sig
45m	83.425	4.523	68.225	3.008	<0.001	Sig
60m	82.45	5.144	70.65	5.177	<0.001	Sig
75m	82.525	4.0	69.225	3.46	<0.001	Sig
90m	81.95	5.119	71.025	3.99	<0.001	Sig
105m	80.125	4.369	70.775	2.423	<0.001	Sig
120m	78.95	7.871	73.9	6.267	0.002	Sig

Inference : In study group ,while comparing the control group there was a significant decrease in diastolic blood pressure intraoperatively, during infusion, and recovery period and post extubation time.

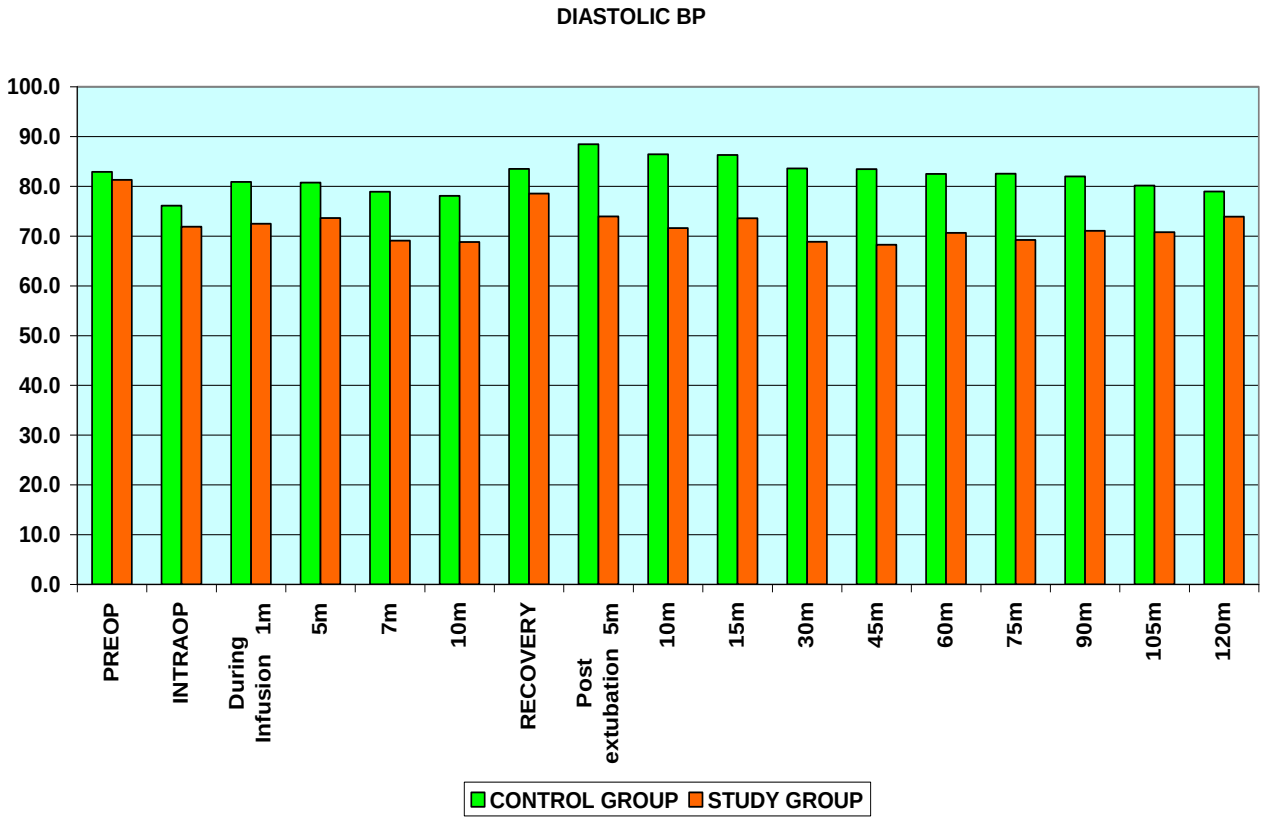

DIASTOLIC BP
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
PREOP
INTRAOP
During Infusion 1m
5m
7m
10m
RECOVERY
Post extubation 5m
10m
15m
30m
45m
60m
75m
90m
105m
120m
CONTROL GROUP
STUDY GROUP

TABLE – 6

MEAN ARTERIAL PRESSURE

MAP	CONTROL GROUP		STUDY GROUP		p value	Significance
	MEAN	SD	MEAN	SD		
PREOP	98.425	9.718	96.067	9.182	0.268	Not sig
INTRAOP	89.908	6.572	87.083	6.732	0.061	Not sig
During Infusion 1m	95.683	4.721	86.692	5.974	<0.001	Sig
5m	95.033	4.978	87.142	6.54	<0.001	Sig
7m	92.9	5.008	82.692	4.869	<0.001	Sig
10m	91.675	5.252	82.8	6.307	<0.001	Sig
RECOVERY	101.75	7.72	91.35	4.258	<0.001	Sig
Post extubation 5m	103.75	4.928	86.8	4.26	<0.001	Sig
10m	100.217	4.997	85.833	5.277	<0.001	Sig
15m	99.567	3.779	86.083	5.415	<0.001	Sig
30m	96.85	4.822	81.792	3.412	<0.001	Sig
45m	96.167	3.187	83.05	3.806	<0.001	Sig
60m	95.4	3.641	83.6	4.858	<0.001	Sig
75m	94.15	2.936	82.008	3.8	<0.001	Sig
90m	94.358	4.532	82.858	3.142	<0.001	Sig
105m	92.75	3.837	83.708	2.629	<0.001	Sig
120m	91.15	5.445	85.633	5.488	<0.001	Sig

Inference: In study group ,there was significant decrease in mean arterial pressure during recovery and post extubation period when compare to control group.

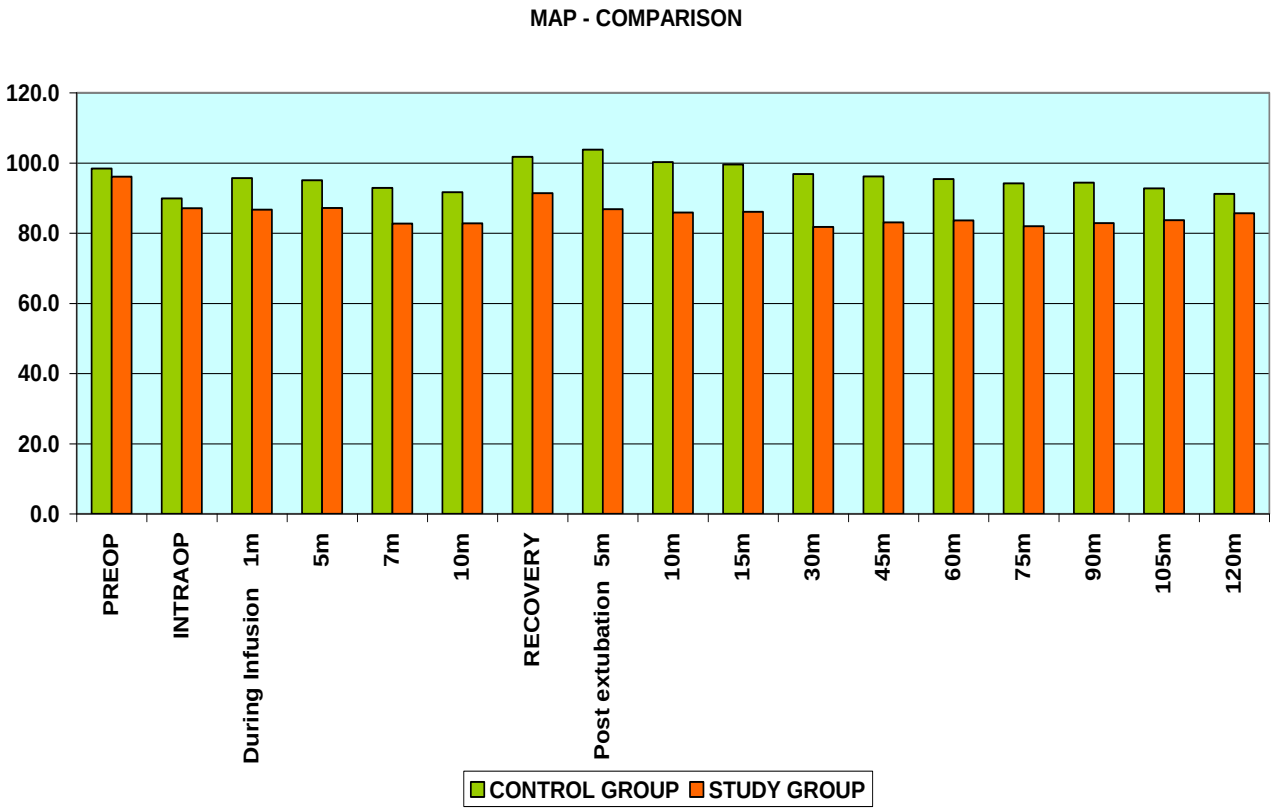

MAP - COMPARISON
120.0
100.0
80.0
60.0
40.0
20.0
0.0
PREOP
INTRAOP
During Infusion 1m
5m
7m
10m
RECOVERY
Post extubation 5m
10m
15m
30m
45m
60m
75m
90m
105m
120m
CONTROL GROUP
STUDY GROUP

TABLE – 7

SPO2 COMPARISON

SPO2	CONTROL GROUP		STUDY GROUP		p value	Significance
	MEAN	SD	MEAN	SD		
PREOP	99.275	0.716	99.225	0.768	0.764	Not sig
INTRAOP	99.375	0.838	99.325	0.859	0.793	Not sig
During Infusion 1m	100	0	100	0	1	Not sig
5m	100	0	100	0	1	Not sig
7m	100	0	100	0	1	Not sig
10m	100	0	100	0	1	Not sig
RECOVERY	99.675	0.474	99.475	0.716	0.145	Not sig
Post extubation 5m	99.85	0.362	99.75	0.543	0.335	Not sig
10m	98.725	0.905	98.875	0.883	0.455	Not sig
15m	99.175	0.874	99.15	0.77	0.892	Not sig
30m	98.725	0.933	98.675	0.944	0.812	Not sig
45m	98.925	0.997	99.025	1	0.655	Not sig
60m	99.45	0.846	99.475	0.751	0.889	Not sig
75m	98.725	0.933	98.775	0.947	0.813	Not sig
90m	99.2	0.823	99.275	0.816	0.683	Not sig
105m	99.2	0.853	99.2	0.791	1	Not sig
120m	96.825	0.958	96.725	0.877	0.628	Not sig

Inference: There was no significant changes in the oxygen saturation in the blood both in control and study groups.

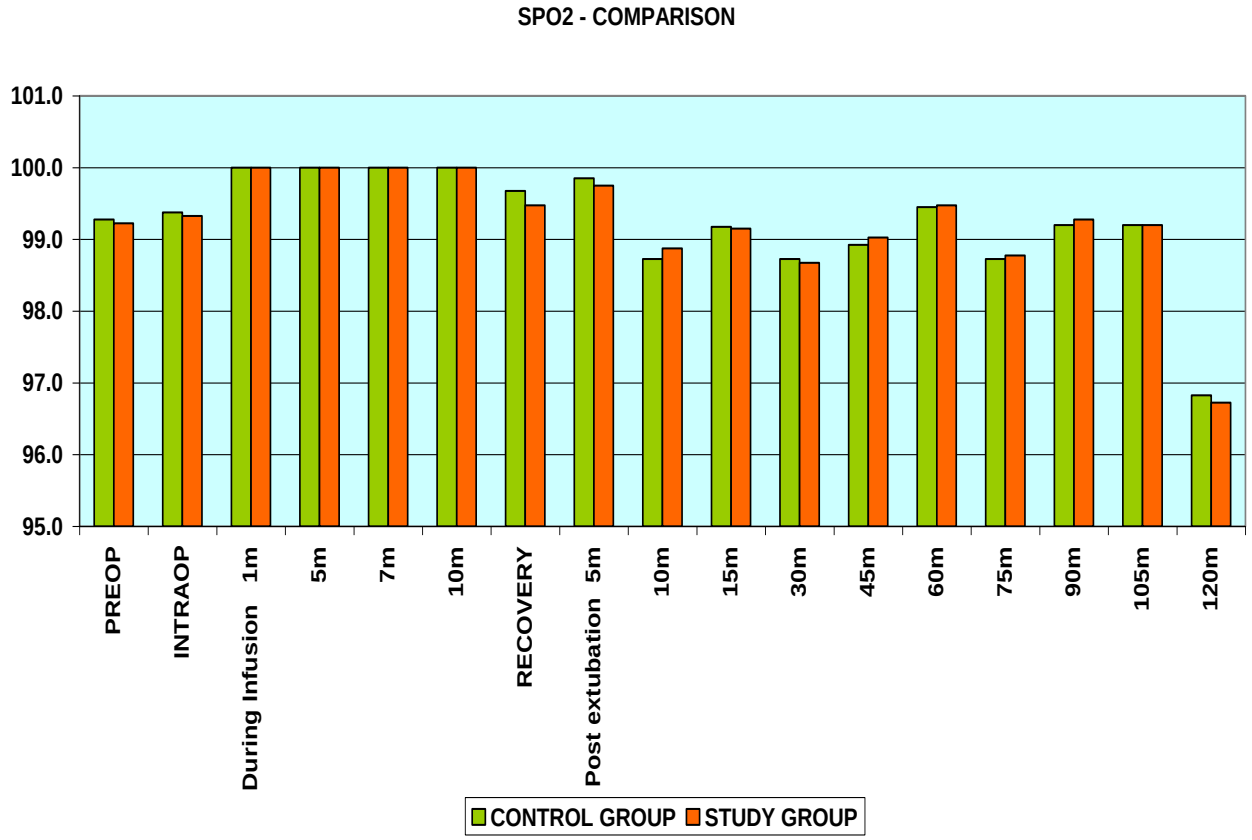
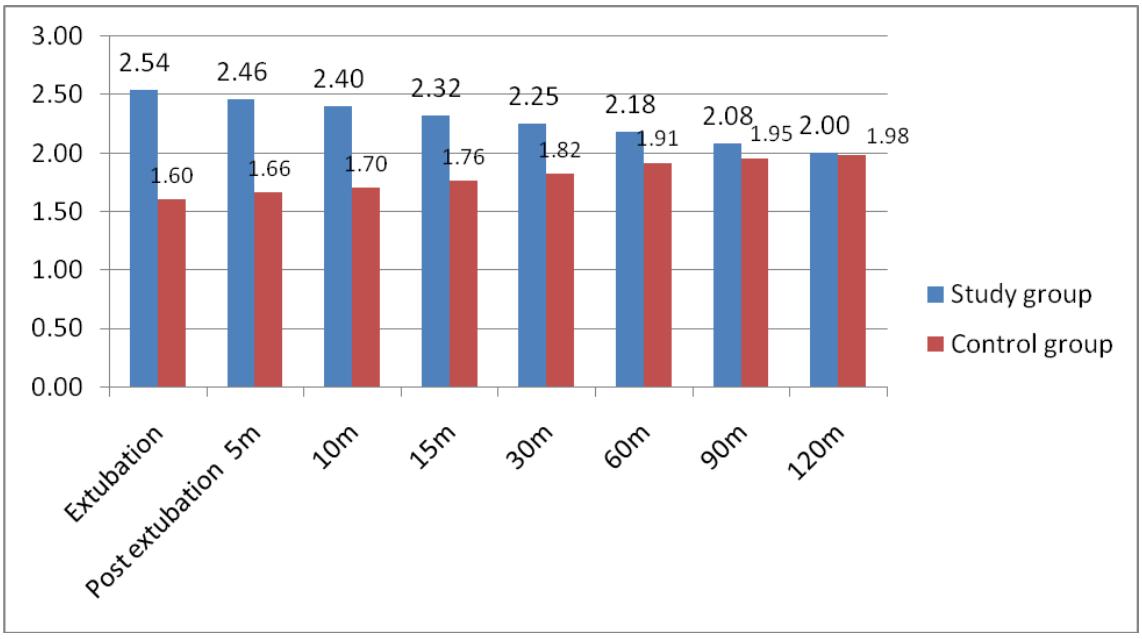

SPO2 - COMPARISON
101.0
100.0
99.0
98.0
97.0
96.0
95.0
PREOP
INTRAOP
During Infusion 1m
5m
7m
10m
RECOVERY
Post extubation 5m
10m
15m
30m
45m
60m
75m
90m
105m
120m
CONTROL GROUP
STUDY GROUP

Table – 8

Sedation score

Sedation score	Study group	Control group	p value	Significance
Extubation	2.54	1.60	<0.001	Sig
Post extubation 5m	2.46	1.66	<0.001	Sig
10m	2.40	1.70	<0.001	Sig
15m	2.32	1.76	<0.001	Sig
30m	2.25	1.82	<0.001	Sig
60m	2.18	1.91	<0.001	Sig
90m	2.08	1.95	0.604	Not sig
120m	2.00	1.98	0.771	Not sig

Score	Study group	Control group
Mean	2.28	1.8
SD	0.68	0.81
P value	0.005 significant	



DISCUSSION

During general anesthesia tracheal intubation and extubation are associated with increases in the sympathetic activity which result in elevated plasma catecholamines levels. This causes an increase in heart rate, blood pressure, myocardial contractility and systemic vascular resistance.

To attenuate these responses during tracheal extubation, various methods have been performed which include use of drugs local anesthetics, antihypertensives, calcium channel blocker beta-blockers inhalational agents and alpha agonists.

There are various studies to evaluate the attenuation of the extubation emergence responses during general anesthesia by using many drugs and I preferred this dexmedetomidine drug at low dose, given as an infusion before the skin closure to attenuate the emergence response during extubation. It is superior to opioids and other drugs that it is a potent central sympatholytic action and analgesic and is less effect on cardiovascular system. It has stable cardiovascular effects.

Demographic factors:

In my observation, there were no significant changes in age, gender selection criteria.

There were significant changes in the following parameters like tachycardia response, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation in control group when compare to study group.

Heart rate:

Tachycardia response is significantly reduced during recovery and post extubation period in Group D, compare to control group. The mean value in control group during recovery period is 98.0 and standard deviation is 11.934 ,but in study group the mean value is 80.5 and standard deviation is 6.076 with in a significant p –value of <0.001. After post extubation period also in control group the mean value is 96.175 and standard deviation is 12.618,when compare to study group both mean value and standard deviation are 78.02 and 5.498 respectively with in a significant p –value of <0.001.

Liyakhath Ali et.al. study the attenuation of Hemodynamic stress responses during emergence from general anesthesia showed that tachycardia response was seen in 84%patients in Group N,

compared to 36% and 8% in Group F and D respectively (p=0.000). Here two drugs were used to attenuate the stress response during emergence.

Blood pressure:

The blood pressure, both systolic and diastolic and mean arterial pressure responses were significantly raised in control group when compared to study group where due to dexmedetomidine infusion these responses were attenuated .

SPO2:

There was no significant changes in both groups.

Sedation score :

Sedation score was significantly higher in demedetomidine group when compared with normal saline group but not exceed the higher limit. p value <0.001 significant.

Complications :

Bradycardia and hypotension were seen in dexmeditomedine group

SUMMARY

- In this prospective randomized controlled study conducted in our Government Rajaji hospital Madurai, was done to study the effect of dexmeditomidine on haemodynamic responses during emergence from general anaesthesia.
- 80 adult patients of ASA I, II undergoing elective abdominal surgeries were allocated into two groups, 40 in each group. Group A is control group, group D is dexmedetomidine group .
- We assessed haemodynamic responses (Heart rate, systolic and diastolic blood pressure, SPO2) during intra operative period, recovery and post extubation period.
- We found there is no significant difference in demographic data between the two groups.
- The Tachycardia response is significantly reduced during recovery and post extubation period in Dexmeditomidine group, compare to control group.
- The blood pressure, both systolic and diastolic and mean arterial pressure responses were significantly raised in control group when compared to dexmedetomidine group.

CONCLUSION

The present study demonstrates that Dexmedetomidine 0.5µg/kg given before extubation attenuates hemodynamic reflexes during emergence from anesthesia while providing smooth extubation without causing undue sedation but prolongs time to extubation.

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PATIENT PROFORMA

Name:…… IP

no:……..

Age:……. Unit:.....

ASA :

Height : Weight :

Date & Time of Admission : Date & Time of Discharge :

Diagnosis :

Procedure :

History :

Clinical Examination :

Vitals :

PR BP SPO2

System

RS CVS P/A CNS

Basic Investigations:

a) Complete blood count

b) Blood grouping & typing

c) BT, CT

d) Urine routine

e) Blood urea

f) Sr. Creatinine

g) RBS

h) Sr. Electrolytes

i) X ray Chest, j) ECG k) ECHO

Anaesthetic technique :

General anesthesia with controlled ventilation

Complications if any

Duration of surgery :

Monitoring of vitals

Anaesthetic technique:

a) Procedure : 40 patients posted for abdominal surgery procedure under general anesthesia allocated in two groups.

Group D

(n=40)patients received 0.5microgram/Kg diluted to 10ml normal saline.

GroupC

(n=40)patients received 10ml of normal saline (placebo)prior to extubation.

Evaluation of RR, BP, HR, SPO2 before and intraoperatively during extubation and at the end of the procedure.

Heart rate, SBP, DBP, MAP, SPO2, Sedation score

Pre operative	Intra operative	During infusion (in minutes)				Post extubation (in minutes)								
		1	5	7	10	10	15	30	45	60	75	90	105	120
HR														
SBP														
DBP														
MAP														
SPO2														
Sedation														

Remarks :

Complications :

Cough, laryngospasm, bronchospasm or desaturation if any

Questionnaire to be used for the study

H/o any drug intake

H/o COPD, exertional dyspnoea, CAD etc

H/o any drug allergy

H/o any bleeding / neurological deficit

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.K.Kalaiselvi
Designation	:	PG in MD., Anaesthesia
Course of Study	:	2017- 2020
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A study on the effect of Dexmedetomidine on hemodynamic parameters during extubation in patients undergoing abdominal surgery under general anaesthesia
Ethical Committee as on	:	17.05.2019

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean & Convenor

DEAN
Madurai Medical College
Madurai-20

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Doc.(Neuro), Doc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

31 JUL 2019

URKUND

Urkund Analysis Result

Analysed Document:	Dr. Kalaiselvi Anesth THESIS for plaigarism.doc (D58431632)
Submitted:	11/7/2019 1:11:00 PM
Submitted By:	drkalaiselvi9278@gmail.com
Significance:	8 %

Sources included in the report:

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