

A Dissertation on

**“ORAL CLONIDINE AS A HYPOTENSIVE AGENT
IN FESS SURGERY”**

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PROFORMA

MASTER CHART

INTRODUCTION

The recent past has seen an enormous surge in Endoscopic Surgery of the Paranasal Sinuses. The nasal mucosa is rich in blood supply, hence impaired visibility ensues owing to excessive bleeding, leading to a prolonged surgical time. To avoid such complications, Endoscopic Sinus Surgery can be performed either with local anesthesia²³, with vasoconstrictors (e.g. Epinephrine, Cocaine and Phenylephrine^{7,17,23}), or under general anesthesia supplemented with controlled hypotension¹². Several reports have been recorded regarding various techniques for diminishing intraoperative bleeding^{27,6,14}. Many ENT surgeons prefer general anesthesia to local anesthesia^{15,5,9}. They are comfortable with hypotensive anaesthesia since the duration of surgery is reduced considerably with an excellent view of the surgical field.

Hypotension maybe induced with drugs and volatile anaesthetics each having its own advantages and drawbacks. For example., severe hypotension may occur due to potent and rapid effects of intravenous antihypertensive drugs³⁰.

Clonidine is a centrally acting α_2 agonist useful as a premedicant. It also decreases the need for analgesic consumption and the usage of

multiple hypotensive agents intra-operatively. Post operative nausea, vomiting and shivering is also reduced. It has antihypertensive property with decreasing sympathetic outflow. The use of drugs such as oral clonidine given before surgery would be desirable to enhance the hypotensive action of an inhalation agent without the disadvantages of intravenous vasodilators^{20,21} and the avoidance of polypharmacy.

AIM

To analyse oral clonidine given as a premedicant in patients undergoing FESS Surgery and its effects;

- 1) As a hypotensive agent
- 2) On intra operative bleeding using a bleeding severity score.
- 3) In maintaining haemodynamic stability intra operatively
- 4) Reducing antihypertensive drug requirements
- 5) As a premedicant for sedation, intra operative and post operative analgesia
- 6) To evaluate the side effects and complications if any that may arise with the use of clonidine

CONTROLLED HYPOTENSION³²

Hypotensive anaesthesia is a technique in which the Blood pressure is reduced to the desired level thereby providing the surgeon with a bloodless surgical field and minimum blood loss negating the need for blood transfusion. The technique entails the controlled lowering of blood pressure and is defined as a reduction of the systolic blood pressure to between 80-90 mmHg. An alternative definition is a decrease in mean arterial pressure (MAP) to 60-70 mmHg in a normotensive patient.

Historical Background

The concept of intentional induction of hypotension to decrease blood loss and improve operative conditions for intracranial surgery was first proposed by Cushing in 1917. Gardner reported on the deliberate decrease in blood pressure in patients undergoing difficult neurosurgical procedures by arteriotomy. The blood removed was kept in heparinized bottles and reinfused at the end of the procedure. "Irreversible shock," tissue hypoxemia, acidosis and overheparinization indicated that the boundaries of physiological trespass were broken down, and the technique was quickly abandoned. Griffiths and Gillies advocated the use of high spinal analgesia to induce hypotension. The major advancement with

normovolemic hypotension was achieved when ganglionic blockade was combined with foot-down tilt. Enderby described the new method as **“controlled circulation with hypotensive drugs and posture to reduce bleeding in surgery”**.

Ganglionic blocking drugs like Trimethaphan, controlled blood pressure by continuous infusion. Its short action was surpassed only by Sodium Nitroprusside (SNP), introduced into clinical practice in 1962. The introduction of Halothane allowed an easier and gentler induction of hypotension with and without ganglionic blockade.

β -Adrenergic blocking drugs were introduced to treat tachycardia. The 1970s witnessed the introduction of Nitroglycerin and Labetalol as hypotensive drugs and the wider use of induced hypotension in pediatric surgery.

Induced Hypotension has also been referred to as deliberate or controlled hypotension.

Uses of hypotensive drugs

Hypotensive drugs are used to achieve one or more of the following goals.

- (i) Reduction of blood loss,
- (ii) Facilitation of vessel surgery, and
- (iii) Improvement of myocardial performance by reducing the preload and afterload.

When hypotensive drugs are used to reduce blood loss, the blood pressure is deliberately lowered to hypotensive levels to achieve the desired response.

Reduction of blood loss

By producing a relatively dry operative field, Induced Hypotension improves visualization and allows the accurate delineation of lesions. There is less trauma inflicted on nerves, vessels, and delicate tissues. Hypotension may increase the viability of pedicles and grafts and may diminish the incidence of postoperative hematoma, sepsis, and fibrosis. There is less need for (or avoidance of) allogenic blood transfusion. In certain operations, the need for infiltration with epinephrine (adrenaline) containing solution may be eliminated, thereby allowing delicate surgery to be performed without distorting the anatomy. Induced hypotension may also decrease operative time.

Effects on cardiac output and regional blood flows

The cardiovascular effects of hypotensive drugs may be modified by many factors: the anesthetic and adjuvant drugs, posture, degree of hypotension, intrathoracic pressure, acid-base status, circulating, blood volume, age and change in preload and afterload.

- (i) **Cardiac Output:** Vasodilators alter the Cardiac Output through changes in stroke volume and heart rate. They decrease afterload lowering arterial impedance and reduce preload by increasing venous compliance.

Sodium Nitroprusside -induced hypotension is associated with either increased or unchanged Cardiac Output. In contrast, Nitroglycerin, because of its effect on venous capacitance and venous pressure, decreases ventricular filling pressure and, ultimately, reduces Cardiac Output. Hypotension secondary to ganglionic blockade has variable effects on Cardiac Output.

Induced Hypotension rarely, is followed by organ damage. As long as mean arterial blood pressure exceeds the sum of colloid osmotic pressure plus venous pressure, the circulation should be adequate for tissue needs.

(ii) Coronary circulation: The main factor affecting coronary perfusion is the aortic diastolic pressure. During Induced Hypotension, reduced myocardial work secondary to decreased afterload requires less coronary blood flow. A decrease in the heart rate-systolic pressure product as an index of myocardial oxygen demand has been observed during induced hypotension.

(iii) Cerebral Circulation : With progressive decreases in blood pressure, a corresponding, decrease occurs in cerebrovascular resistance, maintaining normal Cerebral Blood Flow.

Sodium Nitroprusside can abolish cerebral autoregulation and increase Cerebral Blood Flow. Increases in Intra Cranial Pressure are mostly seen during the early stages of Sodium Nitroprusside infusion, especially during rapid infusion rates. Hypocapnia tends to attenuate SNP-induced increases in Intra Cranial Pressure. Similar increases occur during Nitroglycerin-induced hypotension. In contrast Trimethaphan does not usually result in increased Intra Cranial Pressure except when intracranial compression is severe.

(iv) Spinal cord blood flow and function: With the popularity of induced hypotension for the operative correction of scoliosis, there

has been concern that hypotension may decrease spinal cord blood flow and predispose to spinal cord injury, particularly during instrumentation.

If deep anesthesia is used during scoliosis surgery, a more prolonged time may be needed to successfully perform the wake-up test. Furthermore, these higher concentrations of the inhalation anesthetic can interfere with SSEP monitoring.

- (v) **Renal Circulation:** Decreases in renal blood flow occur with moderate decreases in arterial pressures. Below 60mmHg (8kPa), renal blood flow may decrease to the point where urine flow ceases. If Induced Hypotension does not decrease the renal blood flow below the critical value for the kidney, it is unlikely that renal damage will ensue. Renal medullar tissue oxygenation, an index of tissue viability, remains adequate despite a significant reduction in endogenous creatinine clearance during induced hypotension. Since glomerular filtration rate is also not autoregulated during anaesthesia, monitoring the urine output may be useful, especially during prolonged hypotension.

(vi) **Hepatic and Regional Blood Flow:** A 40% decrease in arterial pressure by Sodium Nitroprusside results in a decrease in portal pressure (44%) and portal blood flow (25%) and an increase in hepatic arterial blood flow (13%). Sodium Nitroprusside decreases portal sinusoidal resistance, does not interfere with the ability of the liver to increase hepatic arterial blood flow (in conditions of insufficient portal circulation), and does not lead to hepatic hypoxia.

Techniques of Induced Hypotension

- (i) Physiological techniques.
- (ii) Pharmacological agents.

(i) Physiological techniques

Positioning the patient head up or foot down. A hypotensive response may not be evident in the horizontal position, but subsequent tilting decreases the arterial pressure as a result of peripheral venous pooling. For every 2.5 cm head up tilt there will be a decrease of 2 mm Hg reduction in systemic pressure with an increased venous drainage. The patient should not be tilted too quickly as cerebral autoregulation requires several minutes. A further decrease in arterial pressure can be obtained by a gradual increase in the anesthetic concentration.

(ii) Pharmacological agents

Mode of action of hypotensive drugs

Induced hypotension (in normovolemic patients) can be produced by either a reduction in Cardiac Output (CO) or a decrease in Systemic Vascular Resistance (SVR). The precapillary arterioles contain relatively large amounts of smooth muscle and, thus are the major determinants of resistance.

Hypotensive drugs may be classified into:

- (1) Ganglionic blocking drugs (e.g. Pentolinium, Trimethaphan);
- (2) Direct-acting vasodilators (e.g. SNP, Nitroglycerin, Hydralazine)
 - (a) α -adrenergic blocking drugs (e.g. Phentolamine, Urapidil, Nicergoline)
 - (b) β -adrenergic blocking drugs (e.g. Propranolol, Esmolol),
 - (c) Drugs with combined α -and β -adrenergic blocking actions (e.g. Labetalol)
 - (d) Calcium Channel Blocking drugs (e.g. Verapamil, Nicardipine).

(1) Ganglionic blocking drugs.

Ganglionic blocking drugs compete with acetylcholine for the nicotinic receptors on the autonomic post-junctional ganglionic membrane. The arterioles and venules of the skin and splanchnic viscera have predominantly sympathetic vasoconstrictor innervation, so ganglionic blockade produces vasodilation, increased venous capacitance, and hypotension.

Side effects:

Mydriasis and cycloplegia, which may be misinterpreted in the post-operative neurologic assessment. The Hypotensive action of Trimethaphan has been attributed to ganglionic blockade, a direct effect on vascular smooth muscle, α -adrenergic blockade, and Histamine release.

(2) Direct-acting vasodilator drugs

Direct-acting vasodilator drugs fall into two categories:

- (i) Nitric oxide dependent and
- (ii) Nitric oxide independent.

The vasodilating effects of Sodium Nitroprusside and Nitroglycerin have been explained by their ability to provide exogenous Nitric oxide.

Sodium Nitroprusside exerts its hypotensive action primarily by decreasing Systemic Vascular Resistance whereas the venous effect is minimal, so that Cardiac Output is maintained. In contrast, Nitroglycerin has little effect on arteriolar resistance vessels at lower concentrations, but exhibits relatively pronounced effects on the venous capacitance vessels, which results in decreased venous return, decreased ventricular filling pressures, and, ultimately, reduced Cardiac Output.

Hydralazine

Hydralazine is a direct arteriolar vasodilator. It decreases blood pressure within 10 min by reducing Systemic Vascular Resistance, without changing Cardiac Output. Reflex tachycardia tends to accompany the decrease in blood pressure. The hypotensive effect is more pronounced when Hydralazine is given with an inhalation anesthetic.

(a) β -Adrenergic blocking drugs

Treatment with a β -adrenergic blocking drug prevents the increase in heart rate, CO, plasma renin activity, and catecholamine levels and

blocks rebound hypertension after cessation of Sodium Nitroprusside infusion. Furthermore, the dose requirements of Sodium Nitroprusside are decreased by approximately 40%. Propranolol given in small increments up to 60µg/kg, before or after the hypotensive drug, prevents tachycardia and facilitates the control of blood pressure.

Esmolol-induced hypotension was found to be more effective than Sodium Nitroprusside in producing better operative conditions. Because of the ability to produce severe myocardial depression, these drugs should probably be used as adjuvants rather than as the sole hypotensive agent. The advantages of Esmolol are its rapid onset, titration of action, short duration, and cardioselectivity. The drug may be given in a loading dose of 500µgkg⁻¹ min⁻¹ for 2-4 min and continued by constant infusion at the rate of 300µgkg⁻¹min⁻¹.

(b) Labetalol

Labetalol acts as a competitive antagonist at both α₁- and β-adrenergic receptors.

In patients anesthetized with inhalation anesthetics, Labetalol reduces blood pressure gradually (over 5-10 min) by decreasing Systemic

Vascular Resistance with either no change in heart rate or with bradycardia and a slight or no decrease in Cardiac Output.

Because of its long elimination half-life (3-6h), it may be the preferred drug when prolonged hypotension is required.

Labetalol is given in an initial dose of 0.2-0.4 mgkg⁻¹. Incremental doses (half the initial dose) may be repeated after 5-10 min until the desired hypotension is obtained. Advantages over Sodium Nitroprusside include absence of tachycardia, no increase in Cardiac Output, no rebound hypertension, no increase in intrapulmonary shunt, and no increase in Intra Cranial Pressure.

(c) Calcium channel blocking drugs

Nicardipine and Verapamil exert their hypotensive effects primarily by decreasing SVR. Because **Verapamil produces myocardial depression and delays atrioventricular conduction, it is not recommended for inducing hypotension.** Nicardipine has been successfully utilized as a hypotensive drug. It vasodilates the peripheral, coronary, and cerebral vessels while maintaining the Cardiac Output without tachycardia. Careful titration (10-25µg/kg) is mandatory because it

has an “increasing effect” over time and because the hypotension may be resistant to conventional treatment.

Haemodynamic effects of Hypotensive Drugs:

Sodium Nitroprusside-induced hypotension is associated with increases in heart rate, Cardiac Output, activation of the renin-angiotensin system, and release of catecholamines. In contrast, ganglionic blockade results in less of an increase in circulating catecholamines and no activation of the renin-angiotensin axis. The increased heart rate with ganglionic blocking drugs probably results from parasympathetic blockade.

In response to the initial hypotension, reflex tachycardia, mediated through the baroreceptors, occurs with most hypotensive agents, and results in an increased Cardiac Output and a rise in blood pressure. As a result of sympathetic activation, renin is released from the juxtaglomerular apparatus in the kidney. This acts on α_2 -globulin from the liver to produce the decapeptide angiotensin I, which is converted in the lungs to the octapeptide angiotensin II, a potent vasoconstrictor.

Stimulation of the sympathetic and the renin-angiotensin systems may adversely affect the operative course during hypotension. The increased Cardiac Output can cause bleeding. Rebound hypertension may occur following abrupt termination of the Sodium Nitroprusside infusion. This is most likely to be due to an increase in Systemic Vascular

Resistance secondary to unopposed activation of the sympathetic and renin-angiotensin responses. The consequences of rebound hypertension include wound bleeding, hematoma formation, cerebral edema, cerebrovascular accidents, disrupted cerebral autoregulation, increased myocardial oxygen demand, and pulmonary edema.

Very high levels of circulating catecholamine and angiotensin II may have deleterious effects on myocardial and renal tubular cells and may adversely affect arterial and capillary function.

Techniques advocated to prevent and treat tachycardia/tachyphylaxis are:

- (i) Judicious use of a β -adrenergic blocking drug.
- (ii) Pretreatment with Saralasin, an angiotensin II competitive antagonist, and with Captopril, an oral angiotensin-converting enzyme inhibitor. Pretreatment with Captopril results in lower dosage requirements and prevents rebound hypertension.
- (iii) A 10:1 mixture of Trimethaphan (250mg) and SNP (25mg) in a solution of 5% Dextrose in water has been advocated. The mixture produces hypotension with smaller doses of SNP and Trimethaphan than when either drug is used separately (synergistic effect).

- (iv) **Clonidine, an α_2 -adrenoceptor agonist, reduces the requirement for isoflurane (by 60%) and SNP (by 45%) and substantially reduces the need for Labetalol during induced hypotension. By its central effect within the medulla and hypothalamus, clonidine blocks the increased central adrenergic activity concomitant with the use of hypotensive drugs. Other actions include the inhibition of renin release in the kidney and a reduction in Vasopressin release. The recommended dose is 4-8 μ g/kg given orally 2 hours prior to surgery.**

INDICATIONS FOR CONTROLLED HYPOTENSION IN ANAESTHESIA

Control of bleeding in major surgeries like

- (1) Major Vascular surgery, Coarctation of Aorta, Arteriovenous fistula, Aorto-Pulmonary window and PDA repair.
- (2) Neuro surgery: Intracranial surgery facilitation of intracranial exposure because of better visualization and reduction of brain volume.
- (3) Liver surgeries like lobectomy and Hepatectomy.
- (4) Oncological surgeries.
- (5) Orthopaedic surgeries.
- (6) Microvascular surgeries.

- (7) ENT Procedures like FESS, middle ear surgery.
- (8) Adrenal Tumour surgery.
- (9) Inability to replace blood as in Jehovah witness who refuse blood transfusion.

CONTRAINDICATIONS

Relative contraindications to Induced Hypotension include:

- (1) Pregnancy;
- (2) Infants where blood pressure is difficult to measure;
- (3) Children with cardiac shunts; Systemic Vascular Resistance may increase the Right to Left shunt and cause hypoxemia;
- (4) Significant reduction in oxygen delivery; Anemia, low fixed Cardiac Output and severe lung disease.
- (5) Systemic diseases compromising major organ function like:
 - Renal, cerebral, or coronary artery disease;
- (6) Valvular Heart Disease;
- (7) Haematological Disease:
 - e.g. (i) Patients with Sickle cell disease; where a reduction in Pao_2 due
 - to decreased Cardiac Output may trigger a crisis.

(ii) Uncorrected Polycythemia may increase sludging and thrombosis;

(8) Patients with narrow-angle glaucoma on Ganglionic blocking drugs.

(9) Inexperience and unfamiliarity with the technique;

MONITORING DURING INDUCED HYPOTENSION

(i) Pulse oximeter.

(ii) Invasive & Non-Invasive BP monitoring

(iii) Electrocardiography – 12 Lead ECG

(iv) Central venous pressure monitoring.

(v) Blood Gas Determination (ABG) for adequacy of oxygenation and for metabolic acidosis.

(vi) Temperature monitoring

(vii) Continuous Urine output monitoring

COMPLICATIONS OF CONTROLLED HYPOTENSION

(i) Severe hypotension / rebound hypertension

(ii) Reactionary or secondary haemorrhage

(iii) Delayed haemorrhage after normotension is restored.

(iv) Blurred vision due to rebound hypertension.

(v) Renal disturbance if the blood supply is compromised for a prolonged period, it may cause Acute Tubular Necrosis (ATN).

(vi) Thrombotic phenomenon following sluggish blood flow in the periphery.

(vii) Increased intracranial pressure.

Complications of controlled hypotension can be avoided by inducing hypotension in a gradual manner, maintaining a Mean Arterial pressure (MAP) above 60 mm Hg and by careful vigilant monitoring methods and protocols.

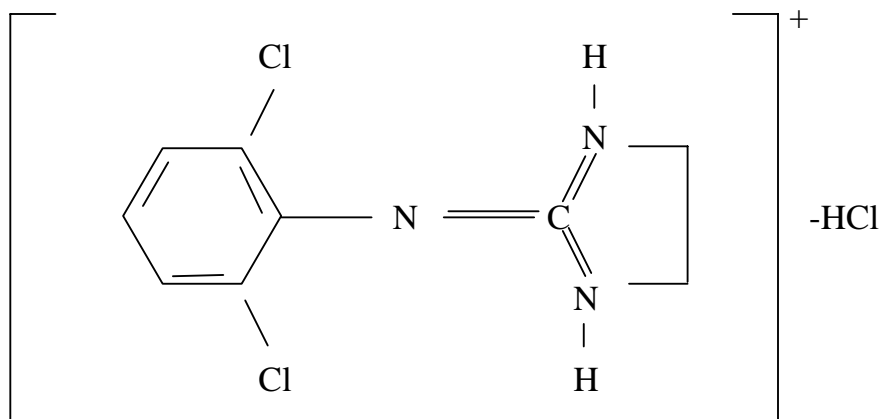
CLINICAL PHARMACOLOGY OF ORAL

CLONIDINE^{4,10,16}

DESCRIPTION

Clonidine hydrochloride is a centrally acting α_2 agonist hypotensive agent synthesized in 1960 for intranasal administration and as a nasal decongestant. Due to its systemic effects (sedation and hypotension) its use as a decongestant has been abandoned.

CHEMISTRY



Clonidine hydrochloride is an imidazoline derivative. The chemical name is (2, 6 - Dichloro - N-2 - imidazolidinylidenebenzenamine hydrochloride).

Clonidine hydrochloride is a white crystalline, odorless powder with a bitter taste. It is produced by chemical synthesis. It is also available in combination with chlorthalidone, triamterene, hydro-chlorothiazide, bencyclane fumarate, or cyclothiazide.

PRESENTATION

1. Oral form-100, 200 and 300 μ g tablets.
2. Transdermal patch – Delivering Clonidine 100 μ g, 200 μ g or 300 μ g daily for 1 week.
3. Parenteral form – An aqueous solution containing Clonidine Hydrochloride 150 μ g/ml. in 1 ml ampoules and is intended for slow intravenous injection to be given as an adjunct with local anaesthesia in regional and neuraxial blocks.

PHARMACOKINETICS

Oral bioavailability 100%

Plasma protein binding 30 to 40%

Peak plasma concentration reached in 60 to 90 minutes

Maximal hypotensive effects 1 to 3 hours after an oral dose.

Elimination half life 6 to 24 hours.

Approximately 50% of the drug is metabolized in the liver to inactive metabolite P-hydroxy-clonidine, while the rest is excreted unchanged by the kidneys. About 20% of the total amount is excreted in the faeces.

EFFECTS OF ACTION OF CLONIDINE

1. CENTRAL NERVOUS SYSTEM

Clonidine by virtue of its action on the small discrete nucleus of noradrenergic cells in the brainstem, the locus coeruleus causes sedation and anxiolysis. Clonidine is a potent analgesic by itself and acts synergistically with concomitant opioids. Anaesthesia induced by α_2 agonists is mediated through G1 protein and is dependant on inhibition of c-AMP production.

2. CARDIOVASCULAR SYSTEM

Action of Clonidine may be classified as (a) peripheral or (b) central.

(a) Peripheral

Clonidine inhibits noradrenaline release from the peripheral prejunctional nerve endings and this may lead to bradycardia. Among the different vascular beds the effects of Clonidine on the coronary circulation is important. Clonidine has been documented to release EDRF (Endothelial derived relaxant factor) in coronary arteries and to enhance coronary blood flow induced by endogenous and exogenous adenosines. Intravenous Clonidine causes a transient hypertensive response due to this direct action on the post-synaptic α_2 receptors. However this effect is soon overcome by a prolonged hypotensive effect due to the more potent inhibitory action of Clonidine on central sympathetic outflow. This effect is not seen when Clonidine is administered orally.

(b) Central

Clonidine mediated hypotension and bradycardia have been well recognized. The mechanism for these actions may involve inhibition of sympathetic outflow and the potentiation of parasympathetic nervous activity. However the precise mechanism involved in these actions is not well understood. While the nucleus tractus solitarius is an important central site for the action of α_2 agonists, other nuclei, including the locus coeruleus, the dorsal motor nucleus of vagus and the nucleus of vagus and

the nucleus reticularis lateralis may also mediate hypotension, bradycardia or both. It has been documented that the imidazole – preferring receptors play an important role in the hypotensive effects of Clonidine.

ANTI – ARRHYTHMIC PROPERTIES

Clonidine prevents adrenaline – induced arrhythmias during Halothane anaesthesia.

3. CEREBRAL CIRCULATION

Clonidine has been shown to decrease cerebral blood flow. This action may be favourable in protecting the brain from an abrupt increase in intracranial tension.

4. RESPIRATORY SYSTEM

Clonidine may produce mild respiratory depression by three mechanisms:

- (i) Sedation or analgesia can produce a small decrease in respiratory rate due to anxiolysis or pain relief.
- (ii) By acting at the α_2 receptors close to the respiratory center in the brainstem.
- (iii) By interference of the thermoregulatory control mechanism.

Nebulized Clonidine attenuates bronchial constriction in asthmatics.

5. ENDOCRINE SYSTEM

Clonidine can decrease stress induced ACTH release and hence cortisol synthesis.

Clonidine activates growth hormone release and hence it has been used as a diagnostic tool to test the pituitary gland's ability to release growth factor in children.

Clonidine also inhibits the release of Insulin from the pancreatic β cells directly.

α_2 agonists decrease circulating Norepinephrine and Epinephrine by central and peripheral mechanism. Centrally they diminish sympathetic outflow by actions in the brainstem and spinal cord. Peripherally, they stimulate classical presynaptic auto inhibitory α_2 adrenergic receptors to decrease norepinephrine release.

6. GASTROINTESTINAL SYSTEM

Hyposalivation is one of the advantages of Clonidine as a premedicant. Clonidine is also supposed to prevent intestinal electrolyte and water secretion in the large bowel.

7. RENAL SYSTEM

Clonidine induces diuresis by:

- (i) Inhibition of Anti Diuretic Hormone (ADH) release.
- (ii) Antagonism of the renal tubular action of ADH.
- (iii) Increase in the Glomerular Filtration Rate (GFR).
- (iv) Release of Atrial Natriuretic Factor.

8. HAEMATOLOGICAL SYSTEM

Clonidine induces platelet aggregation. It also enhances the platelet aggregatory effects of other drugs.

CLINICAL USES

The **advantages** of Clonidine over other adjuvants used in general anaesthesia and regional anaesthesia are:

- (i) Lack of significant respiratory depression
- (ii) Low abuse potential
- (iii) Ability to rapidly reverse therapeutic and pharmacological effects with specific α_2 antagonists.
- (iv) Preservation of haemodynamic stability

- (v) Induced hypotension
- (vi) Limits the use of potentially toxic anaesthetic adjuvant agents.
- (vii) Preservation of renal function in the presence of insult
- (viii) Limits the increase of Intra-Cranial Pressure (ICP) and Intra-Ocular Pressure (IOP).
- (ix) Decrease of narcotic induced muscle rigidity.
- (x) Bronchodilatation

The **disadvantages** of Clonidine over other adjuvants include:

- (i) Dry mouth
- (ii) Sedation / Drowsiness
- (iii) Bradycardia and
- (iv) Hypotension.
- (v) Should be used with caution in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease and chronic renal failure.
- (vi) Clonidine may potentiate the CNS depressive effects of alcohol, barbiturates or other sedating drugs. If a patient receiving Clonidine is also taking tricyclic antidepressants, the hypotensive effects of Clonidine may be reduced necessitating an increase in the Clonidine dose.

- (vii) Due to the additive effect such as bradycardia and heart blocks caution is warranted in patients receiving Clonidine with drugs like Digitalis, Calcium Channel Blockers and Beta Blockers.

USES OF ORAL CLONIDINE IN GENERAL ANAESTHESIA

1. Pre – Medication

As a pre-medicant 90-120 minutes prior to induction produces good sedation, maintains cardiovascular stability intraoperatively without respiratory depression.

Clonidine decreases intraocular pressure both before and during surgery.

Combination of oral and transdermal Clonidine maintains the plasma concentration of Clonidine at therapeutic levels to provide greater haemodynamic stability.

2. Intra-operative Use

The major advantage over other general anaesthetic or supplements is providing haemodynamic stability. Increases in blood pressure and heart

rate during tracheal intubation and surgical stress are blunted or abolished by Clonidine.

Clonidine induced sedation is counterbalanced by reduced requirement of other general anaesthetics and therefore the recovery time is actually reduced.

Clonidine may diminish myocardial ischaemia intra and post-operatively after a single dose, which is beneficial in high risk patients.

Intrathecal Clonidine (150mcg) potentiates local anaesthetic agents. It prolongs spinal anaesthesia with Bupivacaine in elderly patients undergoing orthopaedic surgery.

Postoperative administration of Extradural Clonidine produces effective analgesia in a dose dependant fashion in patients after knee arthroplasty or abdominal surgery.

Systemic Clonidine for postoperative analgesia in the dose of 5µg/kg intramuscularly is very effective.

THERAPEUTIC USE OF CLONIDINE

1. Antihypertensive agent

Clonidine reduces blood pressure in all forms of hypertension with acute and chronic administration. Although normally administered orally a cutaneous patch has also been used. It is enhanced with the addition of a diuretic. In patients with renal failure, renovascular hypertension and pheochromocytoma, Clonidine is an effective hypotensive agent which does not further impair renal function. It can also be used for blood pressure control in patients with hypertension in pregnancy with satisfactory maternal and fetal outcome.

2. Migraine prophylaxis

Clonidine has been used in doses of 50-150 μg daily in the prophylaxis of migraine. Reduction of vascular reactivity has been proposed to explain the role of Clonidine in migraine.

3. Opiate withdrawal syndrome

Clonidine hydrochloride has been used to reduce withdrawal symptoms following cessation of opiates, alcohol, benzodiazepines, and cigarette smoking.

4. Glaucoma

Topical solutions of Clonidine hydrochloride 0.125 – 0.5% reduces intraocular pressure in patients with open-angle glaucoma.

5. Anaesthesia

Clonidine has been used as an adjunct to local and general anaesthesia.

6. Growth hormone screening test

Clonidine as a single oral dose has been used in the out-patient setting as a provocative test of growth hormone secretion in children with short stature. The optimal dose is $100\mu\text{g}/\text{m}^2$ which produces a 7-fold rise in HGH plasma concentration at 60 mins post dosing.

7. Diagnosis of pheochromocytoma

The basis of this test is the ability of Clonidine to inhibit the release of norepinephrine from sympathetic neurons but not from pheochromocytoma cells. Compared to other pharmacological tests for pheochromocytoma (histamine, glucagons, or tyramine

provocation) Clonidine has the advantage of reducing rather than increasing blood pressure.

8. Psychiatric disorders

In Gilles de la Tourette's syndrome, Clonidine appears to have some effect in improving motor and phonic tics and associated behaviour problems.

9. Menopausal symptoms

Clonidine in a dose up to 200 µg daily has been shown to reduce menopausal hot flushes by about 60%.

10. Chronic diarrhea

Clonidine has been reported to be effective in controlling diarrhea in diabetic patients with autonomic neuropathy. Stimulation of α_2 -adrenoceptors on enterocytes, promoting fluid and electrolyte absorption and inhibiting anion secretion, has been proposed as the mechanism of action of Clonidine.

FESS SURGERY²²

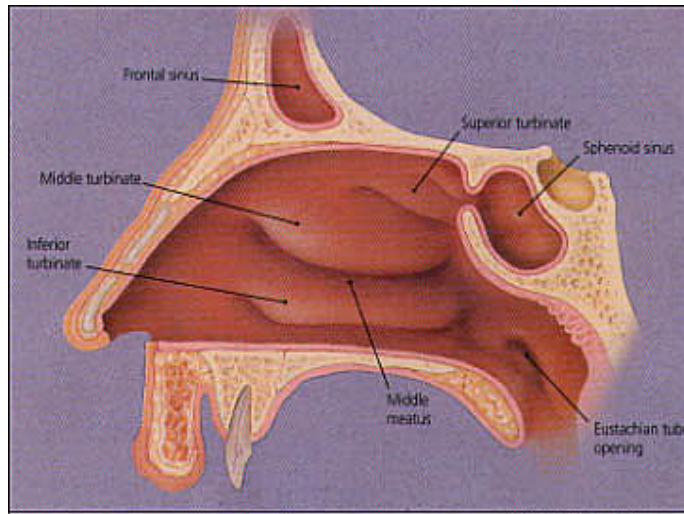
Functional endoscopic sinus surgery (FESS) is a minimally invasive technique in which sinus air cells and sinus ostia are opened under direct visualization. The goal of this procedure is to restore sinus ventilation and the normal function of the nasal sinuses.

CANDIDATES FOR SINUS SURGERY

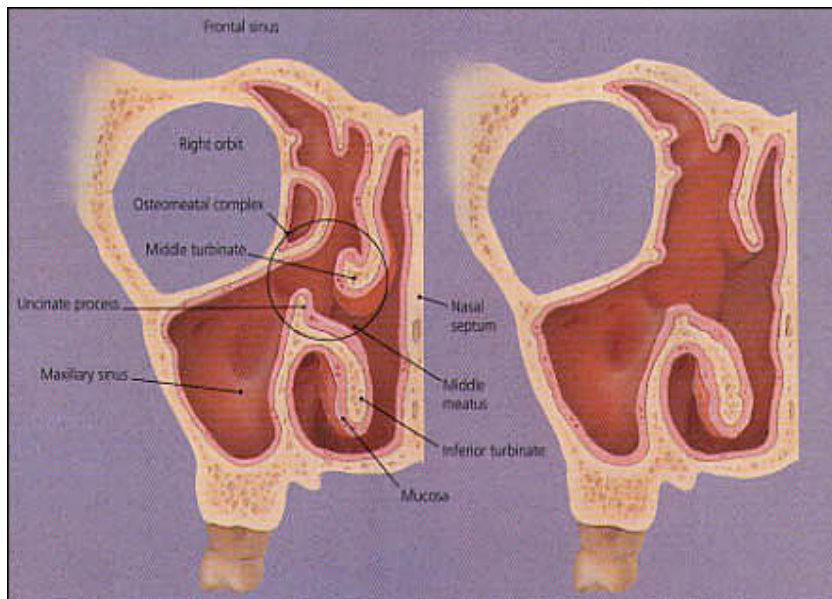
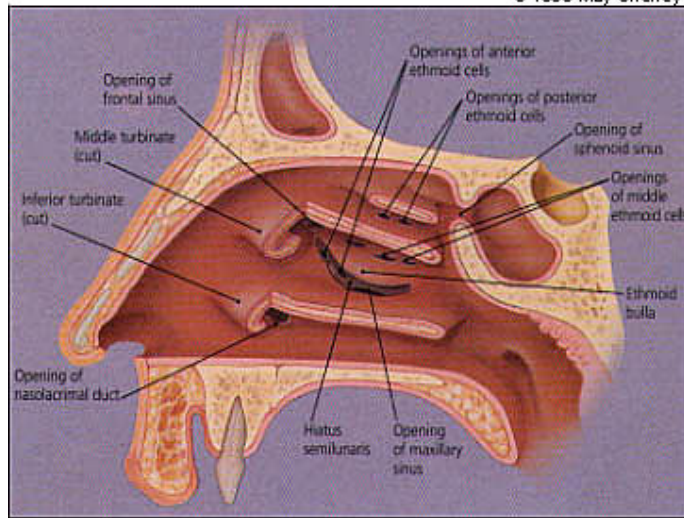
FESS (like any sinus surgery) is most successful in patients who have recurrent acute or chronic infective sinusitis. Patients in whom the predominant symptoms are pain over the maxillary sinus and nasal blockage usually respond well. The sense of smell often improves after FESS surgery.

A CT scan before FESS is mandatory to identify the patient's ethmoid anatomy and its relationship to the skull base and orbit. CT scan defines the extent of the disease, as well as any underlying anatomic abnormalities that may predispose a patient to sinusitis.

Patient selection therefore involves a thorough history and physical examination, a trial with medical treatment and finally, CT scanning. The result is a highly selected group of patients who can expect an improvement of up to 90 percent in their symptoms.



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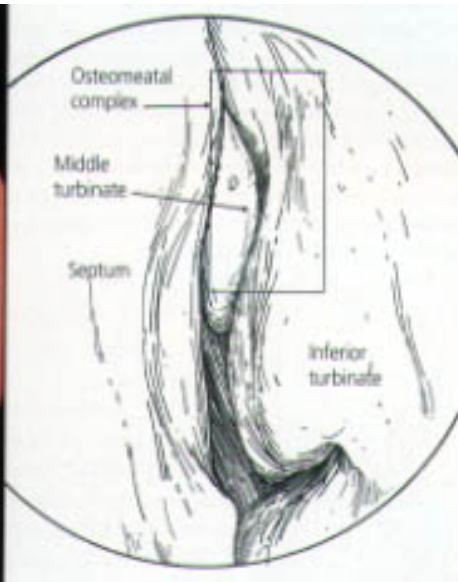
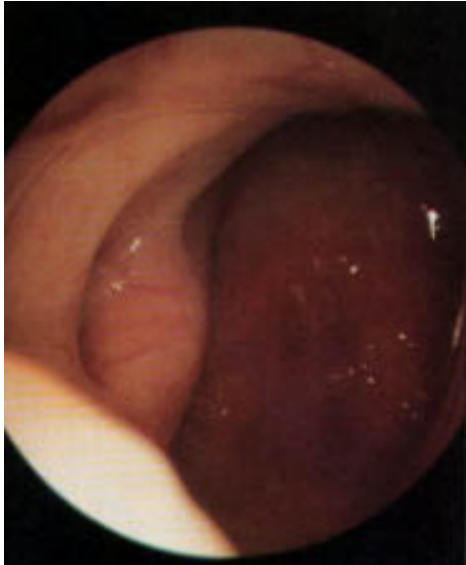
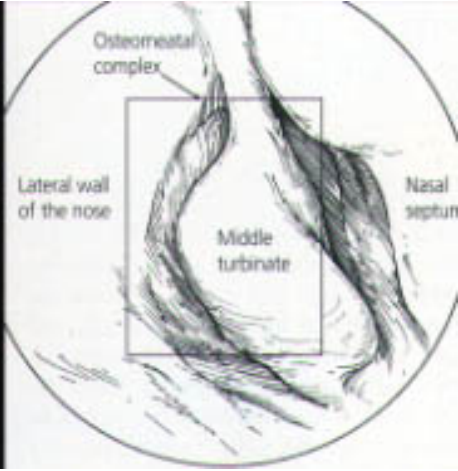
Anatomy of Nasal Turbinates

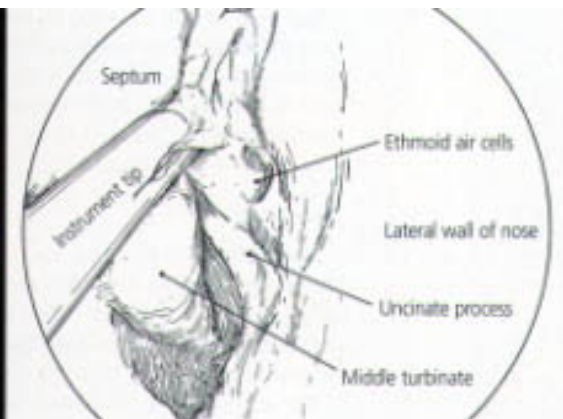
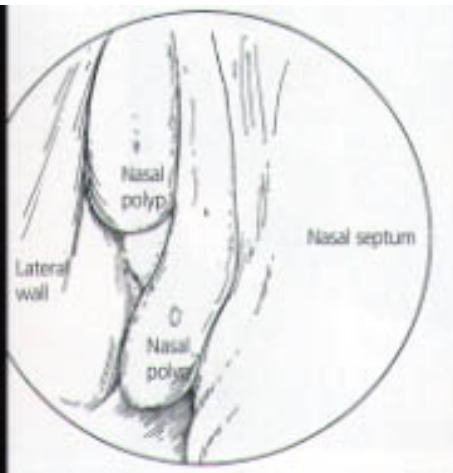
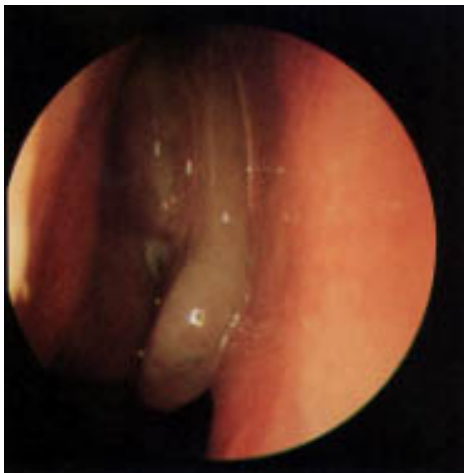
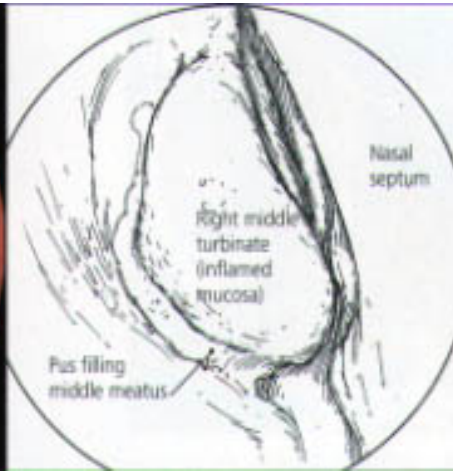
SURGICAL TECHNIQUE

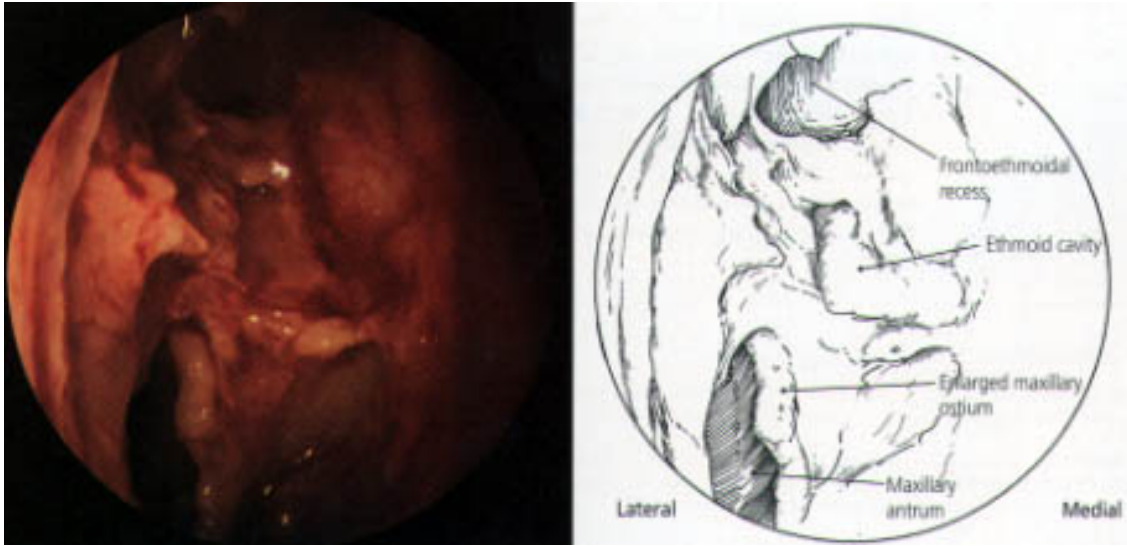
After suitable vasoconstriction using cocaine or ephedrine, the middle turbinate is identified. This is the most important landmark for the procedure. On the lateral wall of the nose at the level of the anterior end of the middle turbinate lies the uncinate process. This is removed, exposing the ethmoid bulla and the opening called the hiatus semilunaris, into which the frontal and maxillary sinuses drain.

The anterior ethmoid air cells are then opened, allowing better ventilation but leaving the bone covered with mucosa. Following this, the maxillary ostium is inspected and, if obstructed, opened by means of a middle meatal antrostomy. This minimal surgery will often be sufficient to improve the function of the osteomeatal complex and therefore to provide better ventilation of the maxillary, ethmoid and frontal sinuses.

Occasionally the CT scan shows disease in the posterior ethmoids and the sphenoid sinus. It is then necessary to continue further into these sinuses. However, in most of the cases, the inflammation is confined to the osteomeatal complex and the anterior ethmoids.







POSTOPERATIVE CARE

Postoperatively, a nasal pack is applied over both the nostrils to reduce the bleeding. Patient is advised to breathe orally. The nasal pack is usually removed after 12-20 hours. It is important to keep the nose as free from build-up of crusts as possible. Nasal cleansing is performed two or three times a week by the surgeon and simple nasal douching carried out several times a day by the patient. Normal function usually returns within one to two months.

OUTCOME

The results after FESS are good, with most studies reporting an 80 to 90 percent rate of success. Good results also have been obtained in patients who have had previous sinus surgery.

REVIEW OF LITERATURE

Literature reviewed to analyse various agents administered during FESS surgery to reduce intra operative bleeding and thereby providing a clear surgical field and also the effectiveness of oral Clonidine as a premedicant to reduce intraoperative bleeding.

- * In 1987, WOODCOCK ET AL³¹, conducted a study with clonidine premedication for isoflurane induced hypotension, the sympathoadrenal responses and a computer controlled assessment of the vapor requirements. **It was found that the mean concentration of 1.4% isoflurane was required to maintain hypotension in the clonidine group compared to 2.3% of the control group.**

- * In 1992, REIGLE ET AL²³, conducted a study with three different vasoconstricting agents in 57 patients undergoing FESS surgery (oxymetazoline Hcl 0.05%, phenylephrine Hcl 0.25% and cocaine 4%). The HR and BP was recorded every 5 to 10 minutes. **It was found that 0.05% oxymetazoline is the preferred vasoconstrictor in patients undergoing FESS surgery.**

- * In 1992, WELFRINGER ET AL³⁰, studied the effects of clonidine premedication and isoflurane anaesthesia to reduce bleeding in otologic surgery in 77 patients. **The comparative assessment of bloodless surgical field quality was in favour of the clonidine group.**

- * In 1995, ANDRE ET AL², compared sodium nitroprusside (SNP) with esmolol in 40 patients as the primary hypotensive agent. **It was found that SNP induced hypotension was poor (due to the vasodilatory effects and tachycardia) when compared with esmolol, which was ideal. (due to unopposed α adrenoceptor effect on the mucous vasculature).**

- * In 1996, FRIEDMAN ET AL⁷, conducted a study of topical bupivacaine for post operative pain in patients who had undergone FESS in 57 patients

- * In 1998 BARRERA ET AL³, studied the perioperative analgesic effect of clonidine administered by the systemic and epidural route in patients undergoing abdominal hysterectomy. He concluded that the epidural route provided post operative analgesia suggesting a spinal site for the analgesic action.

- * In 2000, SUNG.C.S.ET AL²⁶, studied the endocrine correlates of the haemodynamic changes induced by the CO₂ pneuoperitonium and its attenuation by oral clonidine as premedication. **It was concluded that vasopressin and catecholamine, which mediated the increase in SVR was significantly reduced before pneuoperitonium by oral clonidine during laparoscopic surgery.**

- * In 2001, MARCHAL ET AL¹⁹, conducted a study on clonidine and decreases in intraoperative bleeding in middle ear microsurgery, in 40 patients of which 21 received clonidine 90 minutes prior to surgery and 19 received placebo. The end point of anaesthetic management was maintenance of hypotension for a bloodless surgical field. **It was concluded that clonidine reduced bleeding in middle ear microsurgery, attenuated hyperdynamic response to tracheal intubation and reduced isoflurane, fentanyl and urapidil requirements for controlled hypotension.**

- * In 2005, JABALMELI ET AL¹³, studied oral clonidine to reduce intra-operative bleeding in patients undergoing FESS surgery in 113 patients (ASA 1 and 2). 52 patients received oral clonidine 90 minutes prior to surgery and 61 received placebo. **It was seen that clonidine reduced bleeding in FESS surgery and also reduced**

fentanyl and hydralazine requirements for controlling hypotension.

- * In 2003, P. Mandal et. al experimented Isoflurane Anaesthesia for Functional Endoscopic Sinus Surgery, Thirty patients who underwent functional endoscopic sinus surgery (FESS) under general anaesthesia were provided hypotensive anaesthesia (Group I) with isoflurane to facilitate bloodless operative field. The MAP was maintained between 55-60 mmHg. Another group of similar 30 patients were provided normotensive anaesthesia and acted as control (Group II). The mean duration (min.) of surgical procedure was lesser ($p < 0.05$) in group I compared to group II. Similarly mean blood loss (ml) was considerably lower in group I

- * In 2004, G. Tirelli et al., studied Total Intravenous Anaesthesia in endoscopic Sinus-Nasal Surgery, using Remifentanyl and Propofol, or Inhaled using Isoflurane and Fentanyl. It was concluded that the Hypotensive effect of total intravenous anaesthesia and of Isoflurane and Fentanyl was equivalent, but only total intravenous anaesthesia was effective in reducing bleeding during FESS surgery.

- * In 2006, N.M. Elsharnouby et. Al studied Magnesium sulphate as a technique of hypotensive anaesthesia in FESS surgery Magnesium sulphate led to a reduction in arterial pressure, heart rate, blood loss

and duration of surgery. Furthermore, magnesium infusion alters anaesthetic dose requirements and emergence time.

* In 2006, Jian-jun Yang et al, studied Epinephrine Infiltration on Nasal

Field Causes Significant Hemodynamic Changes: Hypotension Episode Monitored by Impedance-cardiography under General Anesthesia, According to the results of the study, it was concluded that local infiltration with low dose epinephrine caused marked hemodynamic changes including decrease in MAP and SVRI, and increase in HR, CI and ACI during FESS under general anesthesia.

MATERIALS AND METHODS

Sixty ASA Class I patients of both sexes between the age of 20 – 40 years weighing between 40 – 65kgs, who were scheduled for elective Endoscopic Nasal Sinus Surgery under General Anaesthesia at Government Stanley Hospital were selected for this study.

This study was designed as prospective randomized comparative study. After receiving the institutional ethical committee approval and informed consent, the patients were allocated into two groups, the clonidine group (C) and the placebo group (P), each group comprising of thirty patients respectively.

INCLUSION CRITERIA

- (i) ASA PS I.
- (ii) Age 20 – 40 years.
- (iii) Weight between 40-65 kgs.
- (iv) Patients undergoing FESS surgery.

EXCLUSION CRITERIA

- (i) Hypertension/ Ischaemic Heart Disease (IHD)/ Rheumatic heart disease.
- (ii) Diabetes Mellitus.
- (iii) Obesity
- (iv) Anticipated difficult airway
- (v) Sinus bradycardia / heart blocks / conduction defects
- (vi) Patients on Antipsychotics
- (vii) Patients on Digitalis, Calcium Channel Blockers and β -blockers
- (viii) H/o CerebroVascular Disease (CVA)
- (ix) Chronic renal disease with increased renal parameters.
- (x) Preoperative Hypotension
- (xi) Patient refusal.

All the patients were informed about the procedure and written consent obtained.

Prof. of ENT Department was informed about the study and his prior permission was obtained.

This study was carried out in the theatre where facilities for Induced Hypotension and Resuscitation were available.

PROCEDURE

PRE-OPERATIVE ASSESSMENT

All the patients were examined prior to surgery. Routine Clinical Examination, Biochemistry Tests, Electrocardiogram and Chest X-Ray were examined thoroughly for the conduct of anaesthesia. Only those patients in the ASA Class I were taken into this study.

NPO duration was eight hours and fluid replacement during Intra operative period was according to the 4 – 2 –1 rule.

Baseline Heart Rate and Blood Pressure both Systolic and Diastolic were recorded prior to pre-medication in both the study groups.

PRE-MEDICATION

Patients were randomly allocated into two groups, Group C (Clonidine) and Group P (Placebo).

Group C patients received oral Clonidine 5 µg/kg with sips of water 90 minutes before surgery. This period ensures maximum plasma concentration after oral ingestion of the drug. Group P patients received placebo drug. All the patients received a nasal packing 2% xylocaine and

1:200000 of adrenaline in order to shrink the nasal mucosal vessels. Injection Glycopyrolate 0.2 mg i.m was given as an anti-sialogogue 45 minutes prior to Induction.

Patients were assessed for level of sedation at 30 minutes, 60 minutes and 90 minutes after pre-medication. The following score was used to assess the **Degree of Sedation**.

Grade 1: Awake and alert patient.

Grade 2: Awake and calm lying down quality.

Grade 3: Drowsy, arousable on oral commands.

Grade 4: Drowsy, arousable on mild physical stimuli.

Grade 5: Drowsy, arousable on vigorous physical stimuli only.

90 minutes after pre-medication the patients were shifted to the operating theatre. Intravenous cannulation was secured and a maintenance infusion of 5% Glucose Normal Saline was started and infusion adjusted at a rate of 8 to 10ml/kg/hour.

Monitors used were:

- (i) Electrocardiographic leads,
- (ii) Non-invasive blood pressure – sphygmomanometer cuff, and
- (iii) Pulse oximetry.

CONDUCT OF ANAESTHESIA

Pre-induction Heart Rate and Blood Pressure both Systolic, Diastolic and MAP were recorded. After Pre-oxygenation with 100% oxygen for 3 minutes, anaesthesia was induced with Thiopental sodium 5mg/kg, Fentanyl 2µg/kg and Vecuronium Bromide 0.1mg/kg. Then laryngoscopy was performed and the trachea was intubated after 3 minutes of mask ventilation with 100% oxygen. In all patients ventilation was controlled manually. Anaesthesia was maintained with Nitrous oxide and oxygen (2:1 ratio) and Halothane 0.25 volume %. Vecuronium top-up doses were given as and when required.

Thereafter the Heart Rate and Blood Pressure were measured at 1 and 5 minutes after induction of anaesthesia and through every 5 minutes for the first 30 minutes and then every 15 minutes thereafter intra-operatively.

To maintain hypotension for producing a bloodless surgical field, mean arterial pressure was proposed to be 75 mm Hg. Halothane was administered with a minimum of 0.25 volume % in both the Groups and later given in escalating doses to a maximum of 1 volume % if necessary. If unsuccessful, Intravenous Fentanyl bolus of 2 µg/kg was added. When both the drugs failed to provide the desired target, Injection Nitroglycerin

diluted to a concentration of 100µg/ml and given as a continuous infusion (0.5-10 µg/min). Intraoperative bleeding was assessed according to the **Bleeding severity score given below:** (Jabalmeli Et AL).

- 0 – No bleeding.**
- 1 – Slight bleeding, no suction of blood required.**
- 2 – Slight bleeding, occasional suctioning required, surgical field not threatened.**
- 3 – Slight bleeding, frequent suctioning required, bleeding threatened surgical field a few seconds after suction was removed.**
- 4 – Moderate bleeding, frequent suctioning required. Bleeding threatened surgical field directly after suctioning was removed.**
- 5 – Severe bleeding, constant suction required. Bleeding appeared faster than could be removed by suction surgical field severely threatened and surgery was not possible.**

Surgeons remarks regarding the field of surgery was also noted.

Injection Atropine 0.6mg was given in titrated doses intravenously if the heart rate went below 60 beats/minute. Patients with a MAP below 65mmHg were treated with Intravenous supplements of Inj. Ephedrine 6mg and infusion of Intra Venous (IV) fluids.

REVERSAL OF RESIDUAL PARALYSIS AND RECOVERY

Patients were reversed with Injection Neostigmine 0.05mg/kg body weight and Injection Atropine 0.02mg/kg body weight at the end of surgery.

Extubation was done when there was a good gag reflex to oropharyngeal stimulation by the suctioning catheter, adequate tidal volume as evidenced by the chest movements and reservoir bag.

The adequacy of return of motor power could not be tested clinically in the clonidine group as the majority of these patients were well sedated.

The patients were shifted to the recovery room and supplemented with oxygen through ventimask. They were observed for 60 minutes during which the vital parameters like the Heart Rate, Blood Pressure, SpO₂ and Respiratory Rate were monitored. They were subsequently shifted to the post-operative ward and their vitals were continuously monitored and recorded at 2 hours and 4 hours. Patients were also assessed for post-operative analgesia at 5 minutes, 30 minutes, 2 hours and 4 hours after extubation. **Analgesia was assessed** as follows:

Grade 1: Patient restless and screaming with pain.

Grade 2: Patient complaining of severe pain and demands relief.

Grade 3: Patient comfortable complains of pain on questioning.

Grade 4: No complaint of pain.

The nursing staff were instructed to give Injection Pentazocine 0.5mg/kg body weight intramuscularly when the patient complained of pain in the post-operative period with the grading of 1 or 2.

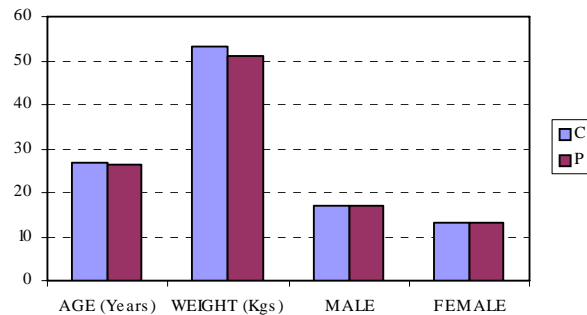
All the patients were observed for 24 hours after surgery for any side effects like nausea, vomiting and dizziness.

OBSERVATIONS

STATISTICS AND ANALYSIS

Sample size of 30 per group was taken for this study. Data was expressed as mean \pm standard deviation (SD) or absolute values. Qualitative data were compared with the Chi square test and fisher's exact test. Quantitative variables were compared with the student 't' test. The level of statistical significance was set at $p < 0.05$.

DEMOGRAPHIC PROFILE



The mean age in Group C was 26.866 ± 4.400 SD and in the Group P it was 26.366 ± 4.0809 SD ($p = 0.649$).

The mean weight in Group C was 53 ± 6.812 SD

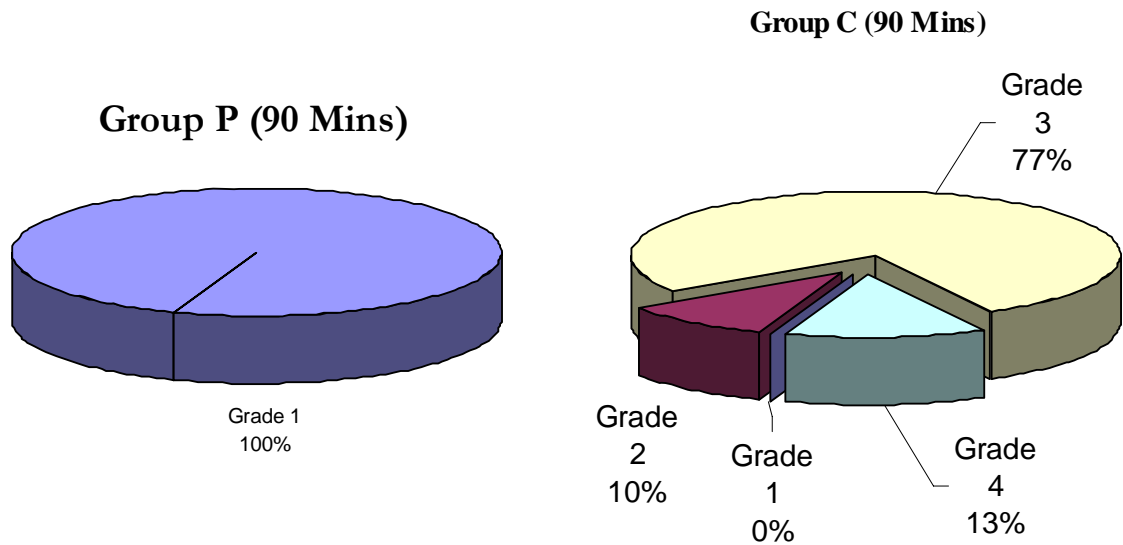
The mean weight in Group P was 51.13 ± 5.475 SD ($p = 0.246$)

Sex distribution in each group was equal Males = 17

Female = 13

Thus the demographic profile was comparable between the two groups. p value not significant.

SEDATION



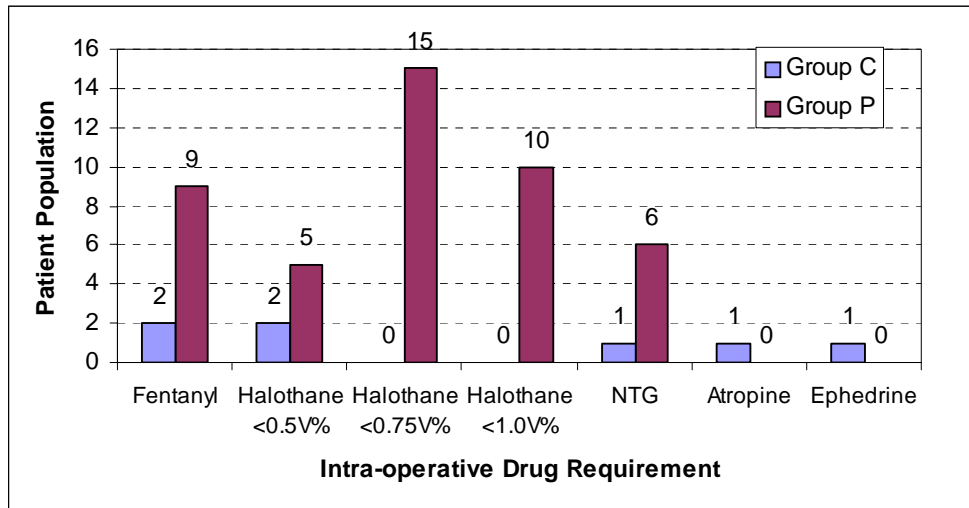
SEDATION SCORE

Score	Grade of sedation and Anxiolysis	30 mins		60 mins		90 mins	
		Group C	Group P	Group C	Group P	Group C	Group P
1	Awake & Alert	4 (13.33%)	30 (100%)	-	30 (100%)	-	30 (100%)
2	Awake, Calm, Lying Quietly	25 (83.33%)	-	4 (13.33%)	-	3 (10%)	-
3	Drowsy Arousable on Oral Commands	1 (3.33%)	-	26 (86.67%)	-	23 (76.67%)	-
4	Drowsy Arousable on Mild Physical Stimuli	-	-	-	-	4 (13.33%)	-
5	Drowsy Arousable on Vigorous Physical Stimuli Only	-	-	-	-	-	-

All the patients were alert at the end of 90 minutes in Group P.

In Group C it was found that 23 (76.67%) patients were in the Grade 3 and 4 (13.33%) patients in the Grade 4 of the sedation score at end of 90 minutes.

INTRA-OPERATIVE DRUG REQUIREMENT



Sl. No.	Drug	30 Mins.	
		Group C	Group P
1	Fentanyl	2 (6.67%)	9 (30.00%)
2	Halothane 0.5 V%	2 (6.67%)	5 (16.67%)
	0.75 V%	0	15 (50.00%)
	1.0 V%	0	10 (33.33%)
3	NTG	1 (3.33%)	6 (20.00%)
4	Atropine	1 (3.33%)	0
5	Ephedrine	1 (3.33%)	0

(i) 9 (30%) of patients in Group P needed top up doses of Fentanyl when compared to 2 (6.66%) of Group C.

(ii) It is hereby seen that a significantly higher consumption of Halothane 0.75 volume % almost 15 (50%) of patients in Group P

and 10 (33%) patients in Group P needed 1 V% of Halothane.

Where as only 2 patients in the Clonidine Group required 0.5 V% of Halothane.

(iii) 6 (20%) of patients in Group P needed NTG infusion (0.1 mg/kg).

While only 1 (3.33%) patient in Group C needed the same.

COMPLICATIONS WITH CLONIDINE

Bradycardia with a Heart Rate < 60 /min. occurred in 1 patient necessitating the use of Injection Atropine 0.6 mg IV. 1 patient developed hypotension with MAP < 65 mm Hg and corrected with IV fluids and Injection Ephedrine 6 mg IV in titrated doses.

HAEMODYNAMIC PARAMETERS

Heart Rate

Sl. No.	Time of observation		HR (Bt/min)	SD	p
1	Baseline	Group C	81.166	4.026	0.154
		Group P	79.633	4.213	
2	Preinduction	Group C	72.8	5.821	0.000
		Group P	91.6	3.45	
3	At Scopy	Group C	75.566	6.463	0.000
		Group P	95.098	18.422	
4	One minute after intubation	Group C	76.601	6.499	0.000
		Group P	94.223	2.721	
5	Five minute after intubation	Group C	80.333	7.871	0.1308
		Group P	85.396	16.294	
6	During extubation	Group C	69.66	14.406	0.63 (NS)
		Group P	85.232	18.436	
7	One minute after extubation	Group C	72.1	10.121	0.000
		Group P	89.03	6.206	
8	Five minute after extubation	Group C	75.533	11.578	0.001
		Group P	84.733	5.051	
9	Thirty minute after extubation	Group C	73.066	15.097	0.052
		Group P	78.795	4.727	
10	Two hours after extubation	Group C	78.333	10.346	0.94 (NS)
		Group P	78.13	124.3	
11	Four hours after extubation	Group C	80.366	8.176	0.0268
		Group P	76.466	4.651	

SYSTOLIC BLOOD PRESSURE (SBP)

Sl. No.	Time of observation		SAP	SD	p
1	Baseline	Group C	123.33	7.111	0.253
		Group P	121.33	6.2881	
2	Preinduction	Group C	106.766	5.864	0.000
		Group P	128	6.643	
3	At Scopy	Group C	112	7.282	0.000
		Group P	133.666	6.149	
4	One minute after intubation	Group C	112.366	6.609	0.000
		Group P	130.733	3.58	
5	Five minute after intubation	Group C	115.766	8.475	0.000
		Group P	125.2	4.859	
6	During extubation	Group C	102.133	9.449	0.0011
		Group P	110.6	6.083	
7	One minute after extubation	Group C	107.266	10.175	0.006
		Group P	113	4.347	
8	Five minute after extubation	Group C	110.966	10.001	0.748
		Group P	111.666	6.477	
9	Thirty minute after extubation	Group C	104.566	9.859	0.001
		Group P	113.33	6.006	
10	Two hours after extubation	Group C	115.066	6.781	0.636
		Group P	114.333	5.04	
11	Four hours after extubation	Group C	118	7.1438	0.356
		Group P	116.337	6.689	

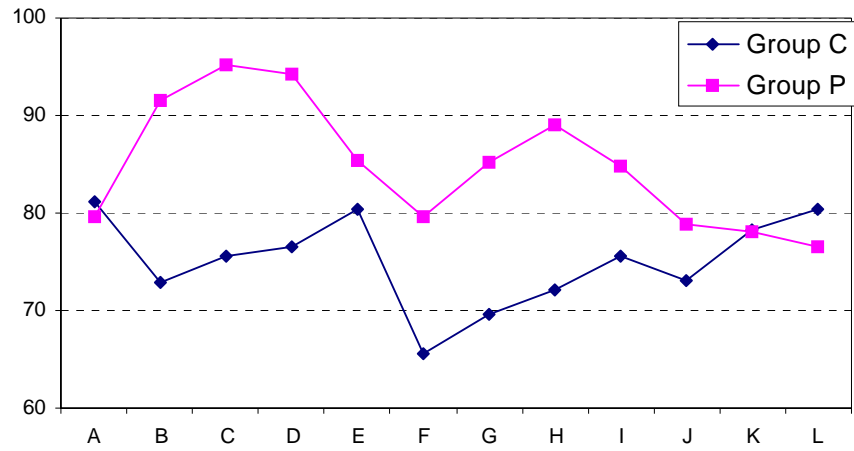
DIASTOLIC BLOOD PRESSURE (DBP)

Sl. No.	Time of observation		DAP	SD	p
1	Baseline	Group C	82	6.102	0.015
		Group P	77.66	7.279	
2	Preinduction	Group C	67.766	5.076	0.000
		Group P	84.333	6.26	
3	At Scopy	Group C	73.333	5.64	0.000
		Group P	91.933	4.346	
4	One minute after intubation	Group C	76.9	6.676	0.000 Wilcoxon sum test
		Group P	117.9	151.701	
5	Five minute after intubation	Group C	80.233	8.81	0.011
		Group P	85.2	5.498	
6	During extubation	Group C	68.733	7.886	0.0002
		Group P	76.533	4.868	
7	One minute after extubation	Group C	68.2	10.626	0.000
		Group P	79.933	5.595	
8	Five minute after extubation	Group C	68.966	10.063	0.000
		Group P	79.533	5.001	
9	Thirty minute after extubation	Group C	66.533	7.682	0.000
		Group P	77.666	4.301	
10	Two hours after extubation	Group C	75.8666	7.295	0.076
		Group P	78.666	4.341	
11	Four hours after extubation	Group C	80	5.872	0.35 (NS)
		Group P	81.333	5.074	

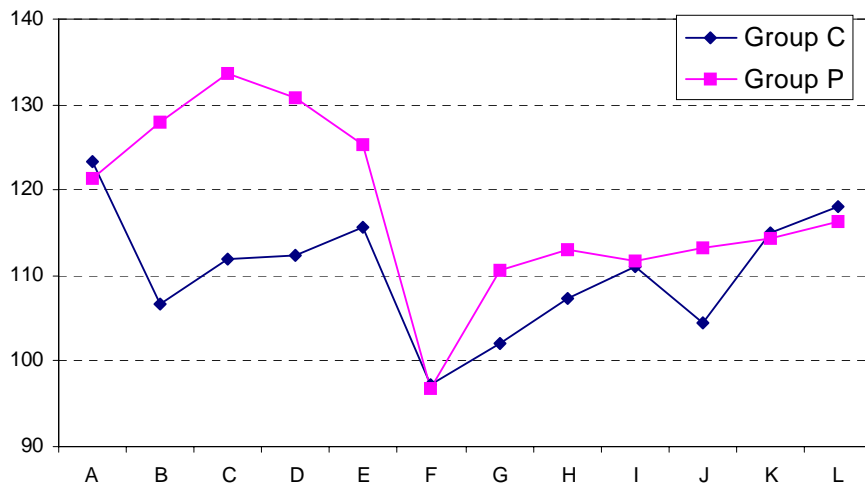
MEAN ARTERIAL PRESSURE (MAP)

Sl. No.	Time of observation		MAP	SD	p
1	Baseline	Group C	95.77	5.174	0.01
		Group P	92.22	5.276	
2	Preinduction	Group C	67.766	5.076	0.000
		Group P	84.333	6.26	
3	At Scopy	Group C	73.333	5.64	0.000
		Group P	91.933	4.346	
4	One minute after intubation	Group C	76.9	6.676	0.000 Wilcoxon sum test
		Group P	117.9	151.7	
5	Five minute after intubation	Group C	92.077	8.342	0.003
		Group P	98.53	4.261	
6	During extubation	Group C	79.866	8.102	0.000
		Group P	87.88	3.408	
7	One minute after extubation	Group C	81.222	10.017	0.000
		Group P	90.955	3.833	
8	Five minute after extubation	Group C	82.966	9.47	0.0003
		Group P	90.243	4.633	
9	Thirty minute after extubation	Group C	79.21	7.726	0.000
		Group P	89.555	3.358	
10	Two hours after extubation	Group C	88.932	6.313	0.2168
		Group P	90.554	3.284	
11	Four hours after extubation	Group C	92.666	4.581	0.7722 (NS)
		Group P	93	4.321	

HEART RATE

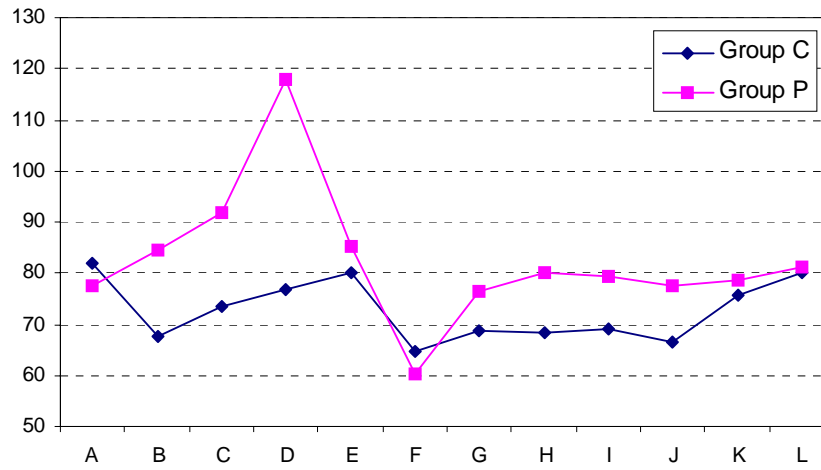


SBP

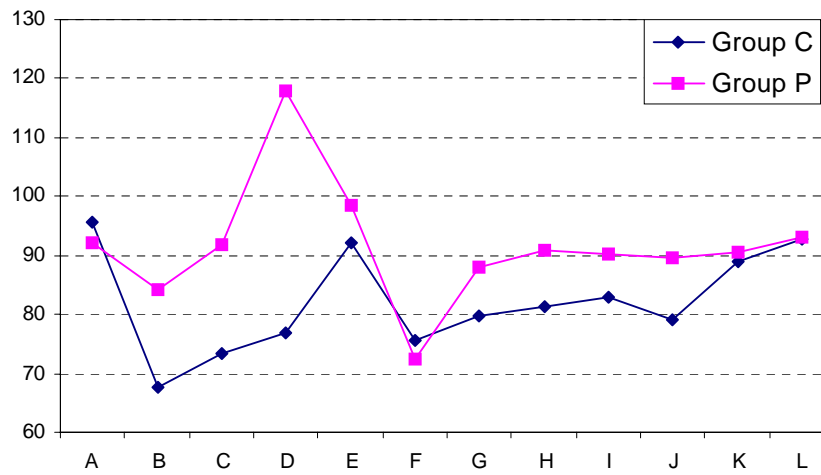


- | | | | |
|---|-------------------------------|---|--------------------------------|
| A | Baseline | G | During extubation |
| B | Preinduction | H | One minute after extubation |
| C | At Scopy | I | Five minute after extubation |
| D | One minute after intubation | J | Thirty minute after extubation |
| E | Five minute after intubation | K | Two hours after extubation |
| F | Average intra-operative value | L | Four hours after extubation |

DBP

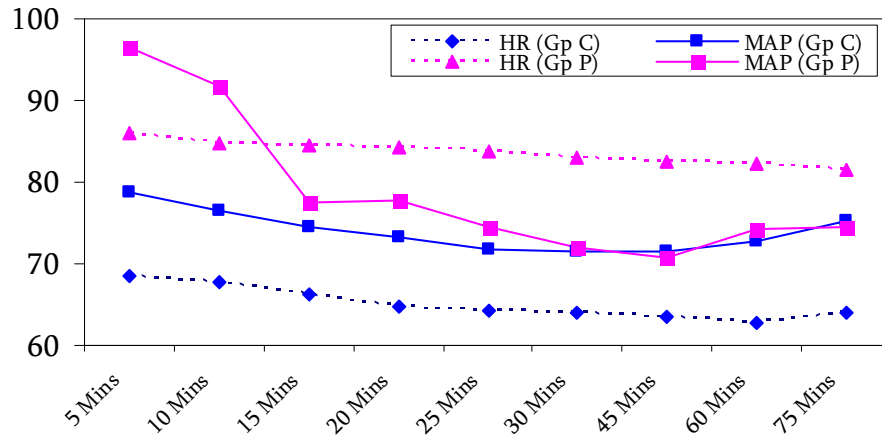


MAP



- | | | | |
|---|-------------------------------|---|--------------------------------|
| A | Baseline | G | During extubation |
| B | Preinduction | H | One minute after extubation |
| C | At Scopy | I | Five minute after extubation |
| D | One minute after intubation | J | Thirty minute after extubation |
| E | Five minute after intubation | K | Two hours after extubation |
| F | Average intra-operative value | L | Four hours after extubation |

Intra-Operative Haemodynamic Parameters



CARDIOVASCULAR PARAMETERS

Mean values of haemodynamic parameters (HR, SAP, DAP, MAP) were taken as pre induction, at scopy 1 and 5 mins thereafter, intra-operatively, at extubation, 1 min, 5 mins, 30 mins, 2 hours and 4 hours thereafter.

INTRA-OPERATIVE PARAMETERS

Haemodynamic stability was remarkable with Group C as seen by the comparisons with Group P. The equivalent stability was maintained in Group P with additional analgesic top-ups, Halothane 0.5-1.0 Vol% and NTG infusion.

The pressor response to both intubation and extubation was blunted in the clonidine group.

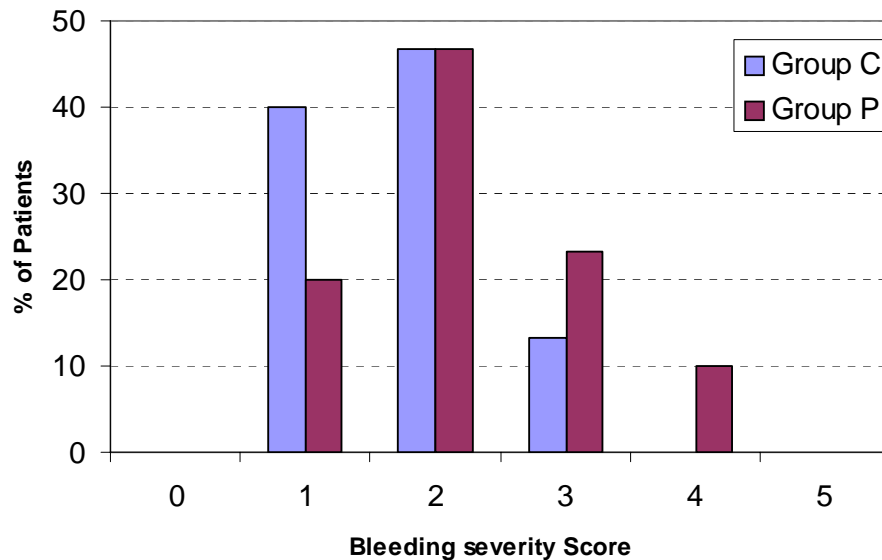
Mean duration of surgery

Group	Minutes	SD
Clonidine	53.33	± 17.137
Placebo	57.166	± 12.844

p = 0.33 [NS]

BLEEDING SEVERITY SCORE

Score	Bleeding severity score	Group C	Group P
0	No Bleeding	-	-
1	Slight Bleeding, No suctioning of blood required	12 (40%)	6 (20%)
2	Slight Bleeding, Occasional suctioning of blood required. Surgical field not threatened	14 (46.67%)	14 (46.67%)
3	Slight Bleeding, frequent suctioning of blood required. Bleeding threatened surgical field a few seconds after suction was removed.	4 (13.33%)	7 (23.33%)
4	Moderate bleeding, frequent suctioning required. Bleeding threatened surgical field directly after suction was removed.	-	3 (10%)
5	Severe bleeding, constant suctioning required. Bleeding appeared faster than could be removed by suction. Surgical field severely threatened and surgery not possible.	-	-



Bleeding graded on the basis of the severity score 3 & 4 was found to be higher in the Placebo Group (7 Patients with a score of 3 and 3 Patients with a score of 4).

Frequency of bleeding severity score of 1 in the Clonidine Group was significantly greater than that of Placebo Group, thus indicating that **bleeding was considerably less in the Clonidine Group.**

However, an equal number of patients in both Groups had a score of 2. This was attained by the use of higher concentration of Halothane and NTG infusions in the Group P.

RESPIRATORY PARAMETERS AND SpO₂ POST OPERATIVELY

All the patients were observed for 24 hours post operatively and it was found that there was no respiratory depression in both the groups. The patients in both groups had a stable cardiovascular status in the post-operative period.

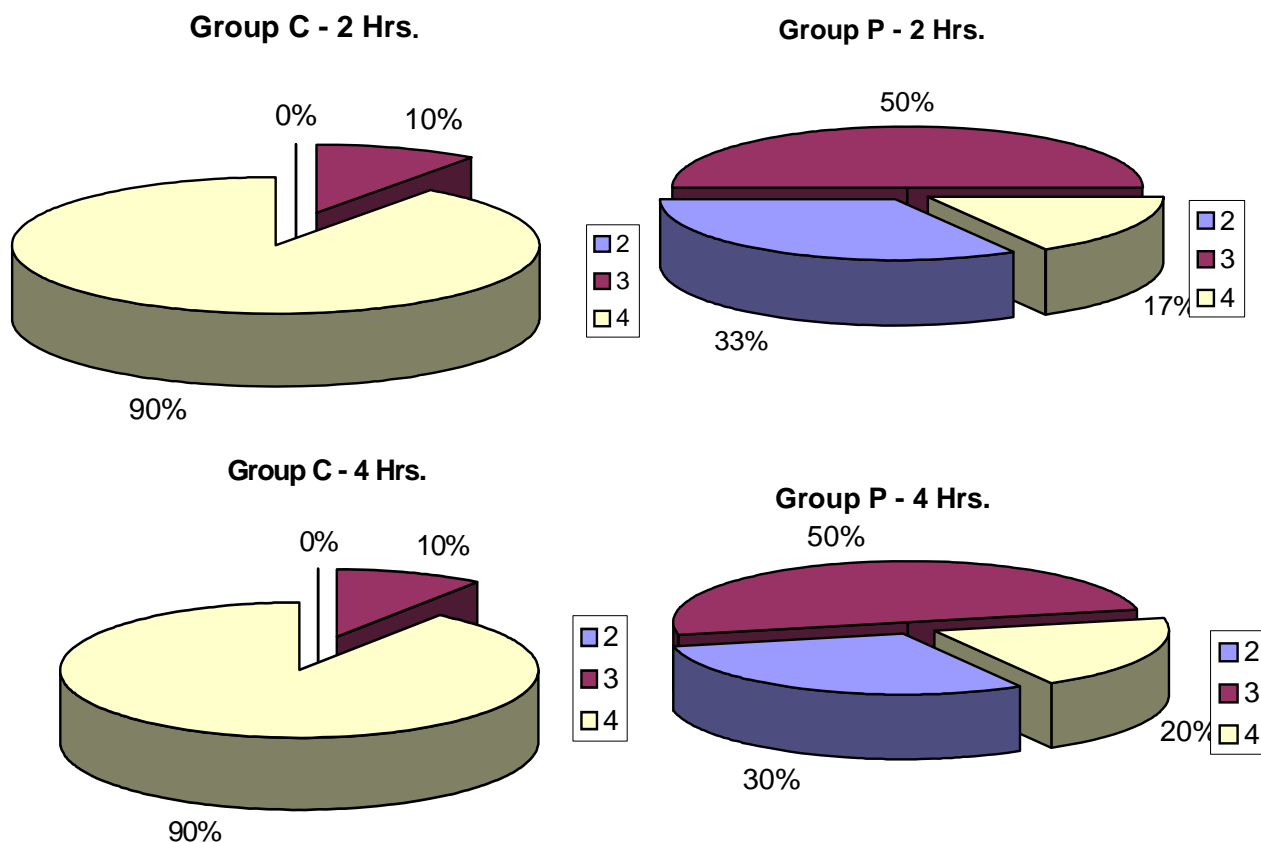
SIDE EFFECTS

Group P: 3 Patients had nausea and 5 patients complained of dizziness post operatively.

Group C: Only 1 Patient had nausea and 2 patients had symptoms of dizziness.

They were treated symptomatically.

POST OPERATIVE ANALGESIA



27 (90%) patients out of 30 had no complaint of pain till 4 hours following surgery in the clonidine group.

15 (50%) out of 30 patients had a grade 3 while 9 (17%) patients demanded relief in the placebo group after 2 hours post operatively.

DISCUSSION

Controlled hypotension is a technique used to reduce bleeding in patients undergoing middle ear surgery, nasal surgery, neuro surgery, orthopaedic surgery, head and neck surgery and plastic surgery. During FESS surgery the single and most common complication is excessive bleeding¹⁵.

Various studies have been done to enable a reduction in bleeding during FESS surgery by using various vasoconstricting agents like Oxymetazoline Hcl (0.05%), Phenylephrine Hcl (0.25%) and cocaine 4%²³ and by the use of Isoflurane³⁰. SNP and Esmolol were also experimented as primary hypotensive agents².

Clonidine an α_2 agonist and a potent suppressor of sympathoadrenal activity was given orally 90 minutes prior to surgery, in an aim to produce hypotension thereby reducing intra-operative bleeding and the duration of surgery. The need for other hypotensive agents was observed to be reduced with Clonidine. All the patients had a very constant and stable Haemodynamic status intra-operatively^{20,21,26,27}. Clonidine suppresses central noradrenergic activity with secondary attenuation of perioperative

hemodynamic fluctuations and stress response as supported by studies done by Pouttu et al²⁰ and Quintin et al²¹.

In this study, the effects of oral Clonidine (5 µg/kg) on intra-operative bleeding in Endoscopic Nasal Sinus surgery was studied. **Bleeding severity score of 3 and 4 was seen to be higher in the Placebo Group than with Clonidine.** These findings were similar to that of Marchal et al¹⁹ and Welfringer et al³⁰ studies.

The Induced Hypotension effect by oral Clonidine directly attributed to reduced bleeding and a good surgical field. **Hypotension was produced in the Placebo Group using higher concentrations of Halothane and NTG infusion.** There was a statistically significant difference in the Halothane requirement of both the Clonidine and Placebo Group. This was in concert with the study of Marchal et al who observed that the intra-operative consumption of Isoflurane was less in patients premedicated with Clonidine than in control patients undergoing middle ear micro surgery. In this study 28 patients belonging to the Clonidine Group attained a MAP of 75 mm Hg with 0.25 V% of Halothane whereas 25 patients in the Placebo Group required concentrations > 0.5 V%. 6 Patients in the Placebo Group were started on NTG infusion to reduce the

MAP. This is also in concert with Marchal et al study on lowered doses of Urapidil to decrease blood pressure in patients given oral Clonidine.

With Clonidine, Fentanyl requirement was also significantly reduced when compared with the Placebo Group. This is attributed to the Pharmacological properties of Clonidine which includes analgesia.

Patients who were given oral Clonidine as a premedicant were well sedated and calm pre-operatively, when compared to the patients in the Placebo Group who were all alert and required additional analgesic top ups and higher concentrations of Halothane.

Extubation was smooth in all the patients of the Clonidine group who were sedated but arousable. Patients in the Placebo Group were sedated and drowsy in the post-operative period thereby requiring a longer observation in the recovery room.

COMPLICATIONS DUE TO THE SIDE EFFECTS OF CLONIDINE

- (i) Bradycardia with a heart rate < 60 /min was encountered in 1 patient and 1 patient developed hypotension with a MAP < 65 mmHG.
- (ii) Only 1 patient had nausea and 2 patients had dizziness.

(iii) It was seen that the Heart rate and Blood Pressure returned to baseline levels only until after 4 hours postoperatively, emphasizing the need for stringent monitoring care in these patients.

SUMMARY

The advantages of Clonidine as premedicant can be summarized as follows:

- * Excellent Sedation and Anxiolysis
- * Attenuation of stress response to laryngoscopy and intubation.
- * Maintenance of intraoperative cardiovascular stability by maintaining Heart Rate and Blood Pressure.
- * Good intraoperative analgesia.
- * Postoperative Sedation and Analgesia.
- * Devoid of Respiratory depression.
- * Less distressing side effects like nausea and vomiting.
- * Easy administration.

Clonidine possesses certain limitations in its usage in patients with bradycardia, conduction disturbances and cardiovascular instability as it is likely to worsen the Cardiovascular status. As it may cause excessive sedation, it is better to be avoided or used with caution in patients with airway obstruction, obesity and extremes of age.

Clonidine at a dose of 5 µg/kg body weight with a ceiling dose of 300 µg is tolerated well by the patients without major complications.

Premedication with oral Clonidine in FESS surgery greatly facilitated controlled hypotension with a clear surgical field which was greatly appreciated by the operating surgeon.

CONCLUSION

The present prospective randomized controlled study shows that Oral Clonidine premedication 90 minutes prior to surgery provides a considerable reduction in bleeding during Functional Endoscopic Sinus Surgery under General Anaesthesia (with 0.25V% Halothane supplementation). It also reduces (almost negligible) the need for other hypotensive drugs to provide a clear field for surgery. Therefore Oral Clonidine can be used as premedicant as well as a hypotensive agent for FESS surgery.

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PROFORMA

Intra Operative Drug requirements

Drugs	Dose (mg)	Frequency
Injection Fentanyl		
Halothane		
NTG Infusion		
Injection Atropine		
Injection Ephedrine		

Post Operative Hemodynamic status, analgesia, respiratory status

Parameters	30 mts	2 hrs.	4 hrs.
HR			
BP			
SBP mmHg			
DBP mmHg			
Analgesic score			
Respiratory Rate			
Spo ₂			
Other observations			
Nausea			
Vomiting			
Dizziness			
Resp. depression.			

MASTER CHART

