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Dexmeditomodine as Anaesthetic Adjuvant to Relieve Stress Response in Gynecological Laparoscopic Surgeries

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INTRODUCTION

DEXMEDITOMIDINE is D-enantiomer of 4(5)-1-2-3-dimethyl phenyl imidazole. It is full agonist at alpha 2c and partial at alpha 2a and 2b receptor. DEXMEDITOMIDINE is a highly selective alpha 2 agonist compared to clonidine with property of sedation, hypnosis, analgesia, sympatholytic and anxiolytic properties, making it an ideal anaesthetic adjuvant. Dexmedetomidine can also be used as anti-shivering agent. [1]

Ever since introduction of Dexmedetomidine in clinical practice in 1999, various studies have been conducted to find use of it in various sub-specialties of anaesthesia.

Utilizing effect on various sites, many studies have been conducted and Dexmedetomidine is presently gaining a lot of popularity. Starting from its use in Intensive Care Unit for sedating even for paediatric patients, use of Dexmedetomidine in regional anaesthesia and to use in general anaesthesia for decreasing requirement for opioids and volatile anaesthetics reducing their side effects have been in the in studies.

Dexmedetomidine is even used for sedation and adjunct analgesia in diagnostic and procedure room, withdrawal/detoxification amelioration in adult and paediatric patients.

When close monitoring of patients is present, Dexmedetomidine can be administered intra operatively safely, according to previous studies. Gynecological laparoscopic surgeries being an entity where hemodynamic variations are present more than even in a normal laparoscopic surgery, it is important to study effect of Dexmedetomidine on hemodynamic parameters like heart rate and blood pressure.

A laparoscopic surgery is preferred by surgeons and patients as it associated with shorter hospital stay, better cosmetic due to small incision, lesser contamination of abdominal content due to less external environment exposure. With all this advantages laparoscopic surgeries pose serious hemodynamic instability. There are significant hemodynamic changes due to pneumo-peritoneum together with surgical stress. Catecholamine, Renin – Angiotensin system and especially vasopressin are released in creation of pneumo-peritoneum thus increasing systemic vascular resistance and arterial pressure. Physiological complications of laparoscopic surgeries have been studied and can be detrimental in patients with cardiovascular compromise. [2] Incidence of post-operative nausea vomiting is more especially in gynecological laparoscopic surgeries.

Anaesthesiologists have tried many drugs to reduce or minimize these cardiovascular changes. Propofol infusions, opioids like remifentanyl. Propofol resulted in overly sedated patients. Opioids has disadvantage of increased post-operative nausea and vomiting and respiratory depression, pruritus.

Dexmedetomidine can be studied instead of other drugs to attenuate stress response during laryngoscopy for intubation, to reduce opioid and anaesthetic drug requirement along with better hemodynamic outcome in intra operative and post-operative period.

AIM OF STUDY

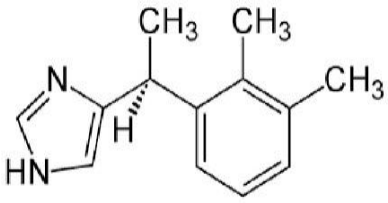
An prospective observational study to monitor mean change in heart rate and blood pressure as a monitor of stress responses after administration of Dexmedetomidine especially after creation of pneumo-peritoneum in ASA1 and ASA 2 patients undergoing gynecological laparoscopic surgery in Medical College Hospital, Trivandrum

PRIMARY OBJECTIVE

To study effectiveness of Dexmedetomidine in reducing stress response in Gynaecological laparoscopic surgeries by monitoring heart rate and blood pressure response.

REVIEW OF LITERATURE

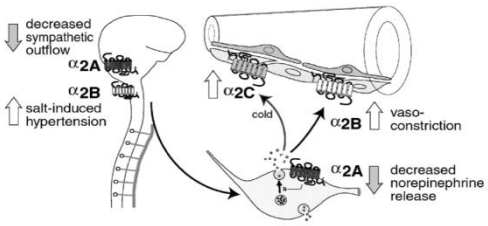
Dexmedetomidine acts selectively on alpha 2 receptors but non-selectively on various subtypes of membrane-bound G protein–coupled α2-adrenoreceptors.[1] Dexmedetomidine is the S-enantiomer of medetomidine, a substance that has been used for sedation and analgesia in veterinary medicine for many years. [3] Like clonidine it belongs to imidazole group of drugs. But it shows a high ratio of specificity for the α2 receptor (α2/α1 1600:1) compared with clonidine (α2/α1 220:1), thus making it a complete α2-agonist. [4]



PHYSIOLOGY OF ALPHA 2 ADRENO RECEPTORS

Alpha 2 adreno-receptors are found in brain, blood vessels, kidney, pancreas, and platelets. [5] Three subtypes of α2 adreno-receptors: α2A, α2B, and α2C.The α2A adreno-receptors are primarily distributed in the periphery, whereasα2B and α2C are in the brain and spinal cord. Postsynaptic α2 adreno-receptors located in peripheral blood vessels produce vasoconstriction, whereas pre-synaptic α2 adreno-receptors inhibit the release of norepinephrine and potentially cause vasodilata-tion. Stimulation of α2 adreno-receptors located in the CNS and spinal cord are involved in the sympatholytic, sedation, and anti-nociceptive effects of α2 adreno-receptors.

Thus overall effect of alpha 2 agonist is sympatholytic rather than vasoconstriction.



Different physiologic functions of alpha 2 adreno-receptors

1. alpha 2a –
   - presynaptic feedback inhibition of norepinephrine release
   - hypotension
   - analgesia
   - sedation
   - inhibition of epileptic seizures
2. alpha 2b-

- Hypertension
- Placental angiogenesis
- Hypertensive effect of Dexmedetomidine
- Analgesia effect of nitrous oxide

3. alpha 2c-

- Feedback inhibition of adrenal catecholamine release
- Analgesic effect of moxonidine
- Modulation of behaviour

HISTORY

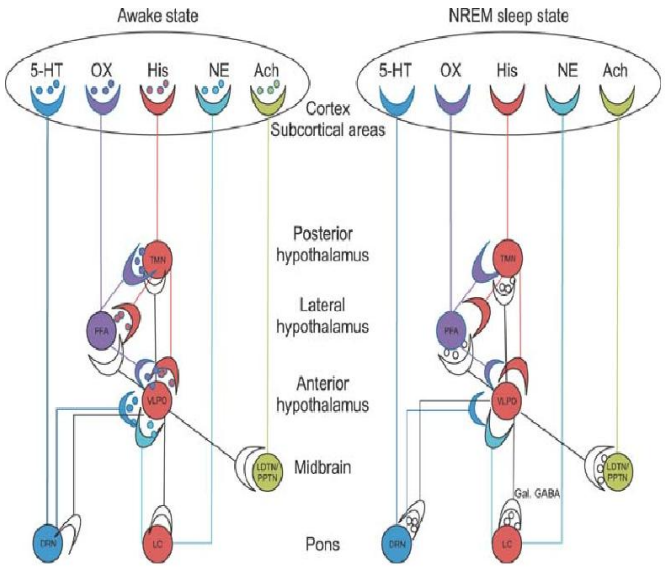
Dexmedetomidine was introduced in clinical practice in the United States in 1999 and was approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult patients in the ICU. But presently Dexmedetomidine is used for prolonged sedation and anxiolytic in the ICU set up, sedation and adjunct analgesia in the operating room and sedation in diagnostic and procedure units, withdrawal or detoxification in adult and paediatric patients [6].

MECHANISM OF ACTION

Dexmedetomidine has action on various region of brain. Main action that produces sedative and anxiolytic effect is by acting on alpha 2 adrenergic receptors at locus ceruleus at brain stem. Action at this site causes decrease sympathetic output from brain and increased firing of inhibitory neurons. The stimulation of the locus ceruleus by Dexmedetomidine releases the inhibition the locus ceruleus has over the ventro-lateral preoptic nucleus.

The VLPO subsequently releases γ-amino butyric acid onto the tuberomammillary nucleus. This inhibits the release of the arousal-promoting histamine on the cortex and forebrain, thus inducing the loss of consciousness. [7] It is like NREM sleep.

Dexmedetomidine acting on dorsal horn of spinal cord produce analgesic effect. [10]



PHARMACOKINETICS

Dexmedetomidine has a p*K*a of 7.1. It is freely soluble in water and is available as a clear isotonic solution containing 100 µg/mL of Dexmedetomidine hydrochloride. Dexmedetomidine is rapidly distributed and extensively metabolized in liver and excreted in urine and feces. Biotransformation involves both direct glucuronidation and cytochrome P450–mediated metabolism. The major metabolic pathways of Dexmedetomidine are direct *N*-glucuronidation to inactive metabolites, hydroxylation mediated primarily by CYP2A6 and *N*-methylation. Hardly any Dexmedetomidine leave body unchanged. Metabolites are excreted via feces and urine.

Dexmedetomidine is 94% protein bound, and its concentration ratio between whole blood and plasma is 0.66. Dexmedetomidine also has effects on cardiovascular variables like blood pressure potentially causing bradycardia, transient hypertension or hypotension, and may alter its own pharmacokinetics .With large doses, marked vasoconstriction occurs and probably affecting its own volume of redistribution .

Elimination half-life of Dexmedetomidine is 2-3 hours. Context-sensitive half-time ranging from 4 minutes after a 10 minute infusion to 250 minutes after an 8 hour infusion.

Clearance rate of Dexmedetomidine with normal patients is 10-30 ml/kg/minute. Apparent volume

of distribution in steady state is 2-3 liters per kilogram. The mean clearance values for patients with mild, moderate, and severe hepatic impairment is 73 percent, 64 percent and 53 percent respectively when compared to the normal healthy subjects. The pharmacokinetics of Dexmedetomidine is not much influenced by renal impairment that is even with Creatinine Clearance of <30mL/minute or extremities of age. [8] In patients with severe renal disease because of decreased plasma proteins, free fraction of Dexmedetomidine is more thus sedative effect will be more. No clinically relevant cytochrome P450–mediated drug interaction has been found. [9]

EFFECT ON CENTRAL NERVOUS SYSTEM

As said in mechanism of action, Dexmedetomidine produces a decrease in activity of the projections of the locus ceruleus to the ventrolateral preoptic nucleus. It results in GABA and galanin release in the tuberomammillary nucleus, producing a decrease in histamine release in cortical and subcortical projections. Thus it reduces excitability of cortical and sub cortical projection. The α2-agonists inhibit ion conductance through calcium channels which are L-type or P-type. This facilitate conductance through voltage-gated calcium-activated potassium channels. Thus Dexmedetomidine decreases depolarization. Dexmedetomidine induces sedation through different receptors than other sedative drugs Propofol and benzodiazepines, which exert their action through the GABA system mainly.

The sedative effect of Dexmedetomidine acts by promoting the endogenous sleep-pathways, thus generating natural sleep patterns.

It's described that it was very easy to wake and having the ability to follow commands and cooperate, while being intubated. Undisturbed, patients were noted to fall asleep momentarily. [10] This characteristic allows for "daily wake-up" tests to be done in a safe fashion. The number of patients experiencing delirium in the ICU is also significantly lower when Dexmedetomidine is used for sedation, when compared with Propofol or lorazepam or with midazolam. Stimulation of the α2C and α2A receptor in the dorsal horn, thus directly suppressing pain transmission by reducing the release of pronociceptive transmitters, substance P and glutamate, and hyperpolarization of interneurons results in analgesic property of Dexmedetomidine. Systemic use of Dexmedetomidine has an opioid-sparing effect during surgery and postoperatively.[11] During general anaesthesia, Dexmedetomidine decreases the MAC of inhaled anaesthetics being used for the procedure be it isoflurane, sevoflurane or desflurane [12] [10d]

When Dexmedetomidine is administered along with local anaesthetic caudally, 1 μg/kg, in children undergoing inguinal hernia repair, response to hernial sac traction is reduced, and there was prolonged postoperative analgesia. [13] Dexmedetomidine administered as an adjuvant to ropivacaine in peripheral nerve blocks shows intensification and foremost prolongation of the sensory blockade. This effect is likely elicited by prolonged hyperpolarization of the un-myelinated C fibers (sensory), and to a lesser extent the A fibers (motor function).

The cerebral protective effects are not well defined. In animal models of incomplete cerebral ischemia and reperfusion, Dexmedetomidine reduced cerebral necrosis. The prevalent idea is that Dexmedetomidine reduces the intra-cerebral catecholamine outflow during injury and modulation of pro-apoptotic and anti-apoptotic proteins. The reduction of the excitatory neurotransmitter glutamate during injury may explain some of the protective effects. In patients undergoing trans-sphenoidal hypophysectomy, Dexmedetomidine had no effect on lumbar cerebral spinal fluid pressure.

Cerebral blood flow velocity at the middle cerebral artery, as measured by trans-cranial Doppler imaging, decreased with increasing concentrations of Dexmedetomidine but carbon

dioxide responsiveness and auto regulation were preserved. The decrease in CBF was not accompanied by a reduction in CRMO2. [14]

In a study of six normal volunteers, the administration of Dexmedetomidine and measurement of CBFV/ CMRe (cerebral blood flow volume divided by cerebral blood flow extraction) ratio was monitored at 6 different intervals.

1) Presedation values
2) Presedation with hyperventilation
3) with plasma level of Dexmedetomidine 0.6ng/ml
4) Plasma level of 1.2 ng/ml
5) 1.2ng/ml in hyperventilation
6) after discontinuing Dexmedetomidine.

It was found that Dexmedetomidine produced the predicted reduction of CBF with a concomitant reduction in CRMO2. CMR-CBF coupling is persevered during Dexmedetomidine administration.[15] Cortical evoked potential amplitudes and latencies were minimally affected when Dexmedetomidine was used intra-operatively. It may also be suitable as an anaesthetic adjunct during surgical treatment of seizures because the epileptiform activity of seizure foci was not reduced by Dexmedetomidine.

EFFECTS ON RESPIRATORY SYSTEM

In spontaneously breathing patients, Dexmedetomidine even at concentrations producing significant sedation reduced minute ventilation; there is no change in arterial oxygenation, pH, or the slope in the carbon dioxide ventilatory response curve. In a study comparing the effects of remifentanyl and Dexmedetomidine on respiratory parameters in normal volunteers, the hypercapnic ventilatory response was unaffected even at doses that produced unresponsiveness to vigorous stimulation. But remifentanyl produced respiratory depression at that high level. Those patients, whom Dexmedetomidine was administered, exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep. Thus Dexmedetomidine sedation is compared to NREM type of sleep.

EFFECTS ON CARDIOVASCULAR SYSTEM

Ebert and colleagues performed a study in volunteers by using a target-controlled infusion system of Dexmedetomidine to provide increasing concentrations (0.7 to 15ng/mL). The lowest two concentrations produced a decrease in MAP (13%) without affecting heart rate followed by progressive increase (12%). Increasing concentrations of Dexmedetomidine also produced progressive decreases in heart rate (maximum 29%) and cardiac output (35%).

The most commonly reported hemodynamic adverse reactions associated with Dexmedetomidine in a phase III trial in 401 patients were hypotension (30%), hypertension (12%), and bradycardia (9%). [19] The initial increase in arterial blood pressure is probably caused by the vaso-constrictive effects of Dexmedetomidine when stimulating peripheral α2 receptors. The incidence of hypotension and bradycardia may be related to the administration of a large IV loading or bolus dose. Omitting the loading dose or not giving more than 0.4 μg/kg reduces the incidence of hypotension or makes it less pronounced. Giving the loading dose over 20 minutes also minimizes the transient hypertension. In several studies after IM and IV administration, Dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/minute) and occasionally sinus arrest or pause.

Generally, these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergic drugs. No rebound effects have been found when discontinuing a Dexmedetomidine infusion, even after giving it for more than 24 hours. Because clonidine and Dexmedetomidine have shown to reduce perioperative oxygen consumption and blunt the sympathetic response to surgery, we can consider that cardiac outcome may be improved. Further studies are needed to prove it.

Gynecological laparoscopic surgeries are done in general anaesthesia with controlled ventilation in the Trendelenburg position. With peritoneal insufflation giving an intra-abdominal pressure of 15mmHg, there are significant increases in partial pressure of carbon dioxide with a decrease in total lung compliance of 25%. This increase in carbon dioxide can be compensated by a small increase in minute ventilation.

Peritoneal insufflation causes major hemodynamic alterations. Three distinct phases of hemodynamic change were demonstrated. Phase one- peritoneal insufflation after induction of anaesthesia resulted in significant increases in systemic venous resistance and central venous pressure and a decrease in cardiac index. Trans esophageal echo cardiography revealed a decrease in ejection fraction of 16% and an increase in end-systolic area of 25%. [16] Thus a ventricular dysfunction can occur during an acute increase in afterload. The initiation of peritoneal insufflation results in a decrease in cardiac output of 25-30% regardless of patient tilt. Also depression in cardiac output remains throughout surgery regardless of surgical stimulation. There is decrease in venous return to the inferior vena cava due to peritoneal insufflation thus the decrease in cardiac output. Right atrial pressure and pulmonary artery pressures increase during pneumo-peritoneum, the consequent increase in intra-thoracic pressure during the pneumo-peritoneum decreases the trans-mural right atrial pressure, thereby decreasing venous return. [17] Systemic vascular resistance has been shown to increase during laparoscopic pneumo-peritoneum. There is increase in intra-abdominal pressure due to compression of intra-abdominal arterioles and the aorta. But the cause for increase in systemic vascular resistance is humoral factors such as catecholamine, prostaglandins, renin-angiotensin, and vasopressin which are secreted by intra-abdominal organs in response to rise in intra-abdominal pressures. The increase in mean arterial pressure despite a drop in cardiac output is explained by the rise in systemic venous resistance. [18] Induction agents depress the myocardium and may reduce cardiac index and mean arterial pressure. Head-up tilt further decreases venous return, as evidenced by falls in pulmonary capillary wedge pressure and right atrial pressure. When the myocardium is depressed, the increase in afterload becomes a significant factor.

The second distinct phase of circulatory response to laparoscopy occurred when the Trendelenburg position was introduced. There is an increased preload which facilitated ventricular function to meet the demands of increased systemic venous resistance, and ejection fraction and Cardiac index.

The third phase was seen at the end of the laparoscopy once Pneumo-peritoneum is released. Hyper dynamic state characterized by an increased heart rate and Cardiac index also a significant decrease in systemic vascular resistance. Hormonal stimulation created by the pneumo-peritoneum ceased, thereby allowing the systemic vascular resistance to fall. Following the pneumo-peritoneum, steep head-up or head-down positions may be used to facilitate surgical view and access. This further will alter venous return and cardiac output accordingly. [20]

Dexmedetomidine used in general anaesthesia offers multiple advantages of anxiolytic, sedation, analgesia and highlight being with no respiratory depression. [21] In a study conducted by A. Arcagel and etal at Catholic University of Sacred hearts, Rome, Italy it was found that Dexmedetomidine offers better hemodynamic stability as there is sympathetic blockade and has anti nociceptive effective. Bradycardia and hypotension are most common and predictable side effect. [22]

In a study conducted at BJMC, Ahmedabad by Patel CR etal on effect of Dexmedetomidine continuous infusion as an adjuvant to general anaesthesia, with entropy study, they concluded that Dexmedetomidine decreases requirement of sevoflurane in maintaining adequate depth of anaesthesia. They took 60 patients randomly

divided them into 2 groups. On group fentanyl was given at dose of 2 microgram per kilogram. Second group was given Dexmedetomidine 1 microgram per kilogram 10 minutes prior to induction. Thiopentone was used for induction.

Maintenance was done with sevoflurane in both groups. Result was sevoflurane used during anaesthesia was much less. At 5 minutes post extubation and 60 minutes post extubation, sevoflurane content in expired gas was much lesser in group which used Dexmedetomidine than group which used fentanyl. Thus they concluded that Dexmedetomidine is better additive in general anaesthesia when compared to fentanyl because of its multiple actions. [23]

Claimed advantages of Dexmedetomidine include minimal respiratory depression with cardio-protection by ensuring hemodynamic stability, neuro-protection and renal protection by decreasing concentration of inhaled anaesthetic, muscle relaxants and opioids used for the procedure, thus making it useful at various situations including offsite procedures. Bradycardia and hypotension are the major side effects observed following Dexmedetomidine infusion. Bradycardia is caused due to reflex response for transient hypertension during initial part of infusion. Subsequent decrease in heart rate is due to decrease in central sympathetic outflow. By meta-analysis by Tan, incidence of bradycardia requiring interventions were increased in studies that used both a loading dose and maintenance doses of Dexmedetomidine in excess of 0.7 microgram/kg/hour. [24] Hypotension is attributed to decreased central sympathetic outflow. Transient hypertensive response has been observed with higher doses (1–4 mcg/kg). This is because of initial stimulation of α-2B receptors present in vascular smooth muscles. This hypertensive episode settles once there is decrease in central sympathetic outflow. [25]

Infusion continued into the postoperative period has been associated with reduced hemodynamics fluctuations and decrease in plasma catecholamine levels.[26] Even following rhinoplasty and neurosurgery, Doses in the range of 0.5 mcg/kg blunted the extubation response and also reduced the emergence reaction. Analgesic requirement to extubation is reduced. There was no delay in recovery or prolonged sedation when boluses were administered before induction or before extubation. Similar was the observation when duration of infusion was within 2 hrs. [27][28]

Dexmedetomidine thus ensures a smooth recovery. Head down position in gynecological laparoscopic surgeries predisposes to airway edema and hyperemia. This discomforting situation to patients is smoothened by use of Dexmedetomidine, without prolonging sedation.

Dexmedetomidine by its sympatholytic action decreases heart rate and blood pressure, thus assessing the depth of anaesthesia by hemodynamic parameters would be unreliable in evaluating its effect on requirement of inhalational agent. Several electroencephalogram- dependent indices such as bi-spectral index and entropy have been used to measure the depth of anaesthesia. Entropy is a useful monitor for measuring the electroencephalographic effects of increasing and decreasing sevoflurane concentration and assessing the depth of anaesthesia. In this study it was found Dexmedetomidine used in patients decreased sevoflurane concentration without affecting entropy. Thus Dexmedetomidine can be used without fear of patient being alert and conscious on operation table. [22]

Dexmedetomidine, when used as sole substitute for remifentanyl in ambulatory gynecologic laparoscopic surgery, provides better peri-operative hemodynamic stability and post-operative analgesia. Time to extubation, to orientation to person, to place and date were shorter in group R (remifentanyl group). Postoperative nausea, vomiting, and analgesic requirements at home were less in group D (Dexmedetomidine group). This study demonstrated that Dexmedetomidine infusion causes a relatively slow recovery with reduced postoperative nausea, vomiting, and analgesic requirements, and similar hemodynamic compared

to remifentanyl in ambulatory laparoscopic surgeries. It may be an alternative to remifentanyl in ambulatory anaesthesia. [29]

Dexmedetomidine provides similar intra-operative hemodynamic response and better post-operative analgesia compared to remifentanyl in patients undergoing supra-tentorial craniotomy.[30]

Dexmedetomidine when administered as infusion at a dose of 0.5 microgram/kg/h has specific analgesic effect and provides visceral pain relief. [31]

In a study conducted at GCS Medical College, Baroda by Dr. Yogesh and Dr.Heena, Dexmedetomidine infusion is simple easy and economic general anaesthetic adjuvant. It also maintains stable hemodynamics and provides excellent recovery. There were sixty patients of either sex scheduled for laparoscopic surgeries and were randomly allocated in double blind manner in two groups. One group receiving Dexmedetomidine 0.4 microgram/kg/hour intravenous infusion with fentanyl, other group received 0.9% saline at same rate with fentanyl. After creation of pneumo-peritoneum, mean value of mean arterial pressure and heart rate were lower in group with Dexmedetomidine. Also there was blunted tachycardia and hypertensive response to intubation compared to fentanyl alone group. Furthermore Dexmedetomidine group had an early and better emergence. [32]

In a study of sixty patients by S Kumar and et al, clonidine and Dexmedetomidine was compared as premedication in laparoscopic surgeries. Result showed both were effective in attenuating the hemodynamic response to pneumo-peritoneum with equal efficacy and without many side effects. They provide reliable postoperative analgesia. Dexmedetomidine provide more duration of analgesia than clonidine. Dexmedetomidine provides more sedation and patient more comfortable with Dexmedetomidine than clonidine. But both drugs are safe to administer for laparoscopic patients [33]

MATERIALS AND METHOD

STUDY DESIGN

PROSPECTIVE OBERVATIONAL STUDY

SETTING

Department of Anaesthesiology, Government Medical College Hospital, Thiruvanthapuram

STUDY PERIOD

12 months

STUDY POPULATION

Patients of ASA 1 AND 2 of age group 18 to 50 years undergoing

Gynaecological laparoscopic surgeries under general anaesthesia

INCLUSION CRITERIA

Patients belonging to American Society of Anaesthesiologists (ASA) grade I and II

Aged between 18 to 50 years

Scheduled for Gynaecological laparoscopic surgeries like laparoscopic hysterectomy, laparoscopic adhesiolysis, laparoscopic recanalization, laparoscopic myomectomy

EXCLUSION CRITERIA

Patients with ASA grade III/IV

Contraindications present to use the drug Dexmedetomidine e.g. liver disorder, renal dysfunction or cardiac disorder.

SAMPLE SIZE

Sample size is calculated using mean value and standard deviation of heart rate from the previous study. Using the formula

$$n = \frac{Z^2_{1-\alpha/2} \times \sigma^2}{d^2}$$

σ = Standard deviation

d = Precision

$1-\alpha/2$ = Desired confidence interval

Applying design effect of 1.5 sample size calculated as 53

METHODOLOGY

53 study subjects are selected from patients posted for Gynaecological laparoscopic surgery under

general anaesthesia after applying inclusion and exclusion criteria. Selected patients are explained about the study and are asked about the willingness to participate in the study. After detailed pre-anaesthetic check-up which includes

- Detailed history taking
- Age and weight measurement
- General and systemic examination
- Airway assessment

Investigations including blood routine examination with platelet count, renal function test, serum electrolytes, ECG, Chest X-Ray, screening markers for HIV, HCV, HbSAg, VDRL Written and valid informed consent is taken.

Patients will be fasting minimum for 8 hours and would be receiving tab alprazolam 0.5 mg and Tab. Pantoprazole 40mg at night on previous day and on the morning of surgery. Two intravenous (IV) lines are put, one for routine fluids and the other exclusively for Dexmedetomidine. Dexmedetomidine infusion should be prepared in normal saline in the concentration of 4 mcg/ml.

Baseline monitors like electrocardiogram (ECG), pulse oximetry, noninvasive blood pressure (NIBP) should be attached. Baseline values of heart rate (HR), saturation (SpO_2), blood pressure (BP) to be noted. Start loading dose of Dexmedetomidine infusion 0.5 mcg/kg and continued for 15 minutes. Premedicate patients with injection glycopyrrolate 4 mcg/kg, Injection midazolam0.02 mg/kg and injection ondansetron 4 mg intravenously (IV). After 15 minutes, change the rate of Dexmedetomidine infusion to a maintenance infusion of 0.2 mcg/kg/h. Induce with Propofol 5 mg IV incremental doses till the eye lash reflex is absent.

Succinylcholine 1.5 mg/kg administered IV to facilitate intubation. Vasopressor response to laryngoscopy and intubation noting HR and BP. Intubate All patients with appropriate sized cuffed endotracheal tube passed orally, and the placement should be confirmed with auscultation and end-tidal carbon dioxide (EtCO2) reading. Maintain anaesthesia with nitrous oxide and oxygen mixture 66:33, and isoflurane, using a closed circuit. Vecuronium is used to maintain intra-operative neuromuscular blockade. Intra-operative anaesthetic requirement should be gauged by hemodynamic parameters every 15 minutes.

Heart Rate and Blood Pressure response to pneumo-peritoneum should be documented and requirement of additional anaesthetic/analgesic to be noted.

Whenever required, anaesthesia was deepened by increasing the isoflurane concentration, followed by Propofol top ups of 10 mg, if needed. Analgesia in the form of fentanyl top ups of 10 mcg. Note any additional requirement of metoprolol or nitroglycerine to control Blood Pressure .Dexmedetomidine infusion to be continued until extubation. Documentation of Hemodynamic response to extubation by observing the pulse and blood pressure should be done.

Document Intra-operative monitoring during the pre-induction, after the loading dose of Dexmedetomidine, at the induction of anaesthesia, during laryngoscopy and intubation, and at pneumo-peritoneum and then every 15 min till the end of surgery and continued during extubation and post operatively of extubation and postoperatively. At the end of surgery, add diclofenac sodium 75 mg to the IV fluid for postoperative analgesia. Note any side effects like hypotension, bradycardia, respiratory depression, postoperative nausea and vomiting. Observe Patients for one hour in the recovery room, and then should be shifted to the ward. Blood pressure is measured with standardized sphygmomano-meter.

Sampling technique-

Simple random sampling

DATA ANALYSIS AND RESULTS

Background Characteristics

Figure Distribution according to age

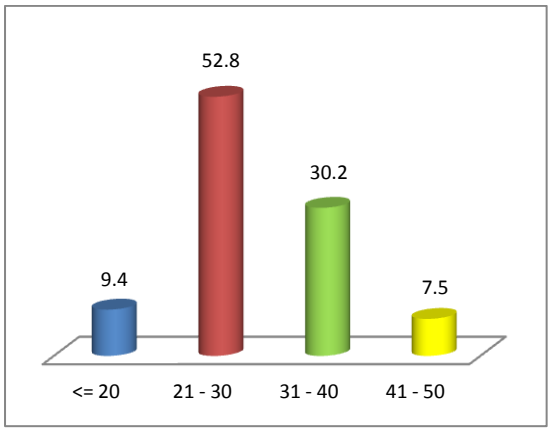


Table Distribution according to age

Age	Count	Percent
<= 20	5	9.4
21 - 30	28	52.8
31 - 40	16	30.2
41 - 50	4	7.5
Mean ± SD	29.2 ± 7.1	

Table Distribution according to ASA PS status

Sex	Count	Percent
Grade I	32	60.4
Grade II	21	39.6

Figure Distribution according to ASA PS status

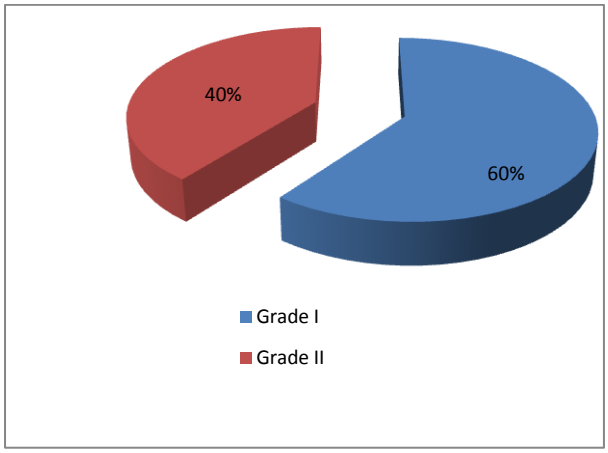


Figure Distribution according to duration of surgery

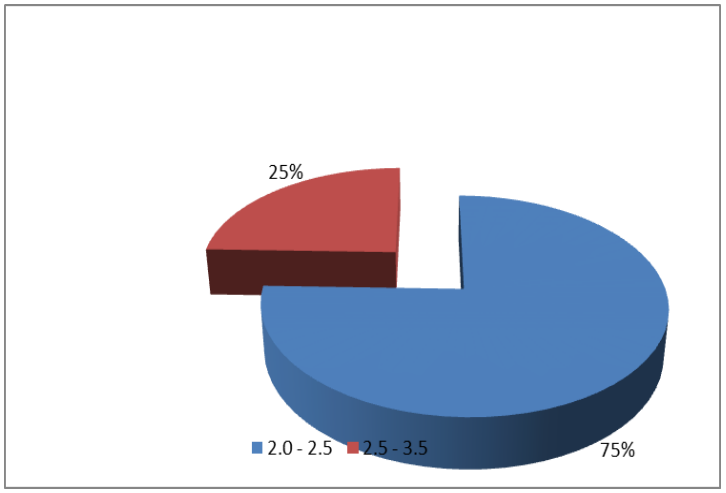


Table Distribution according to duration of surgery

Duration of Surgery	Count	Percent
2.0 - 2.5	40	75.5
2.5 - 3.5	13	24.5
Mean ± SD	2.5 ± 0.4	

Comparison of Outcome Variables

Figure showing Effectiveness of treatment on Heart Rate

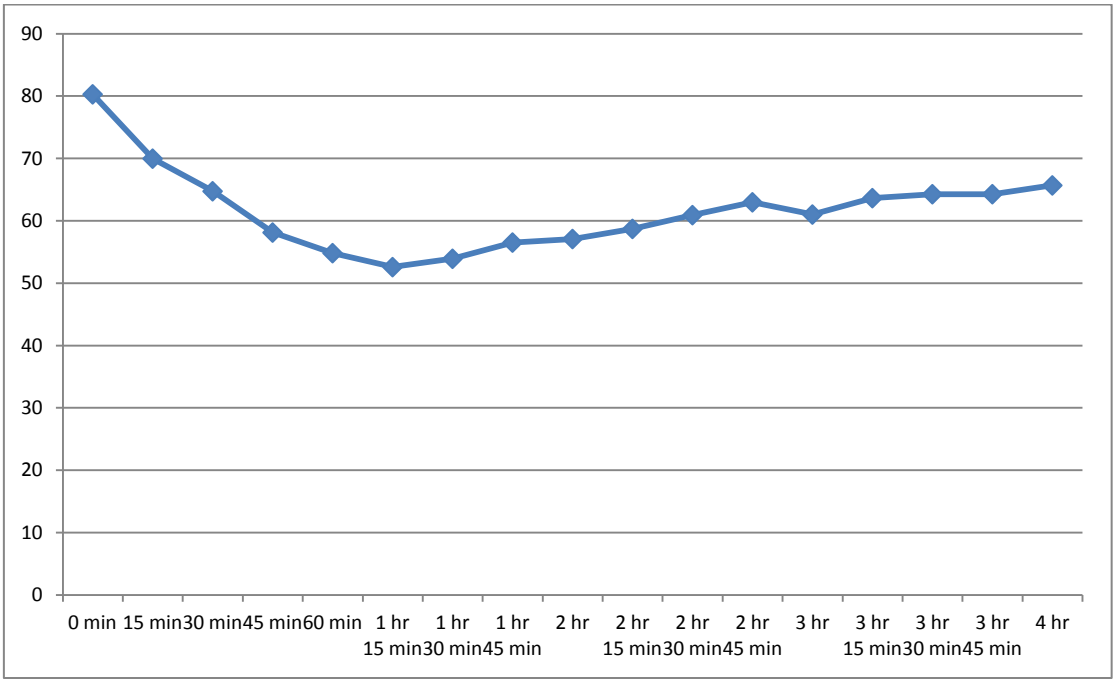


Table Effectiveness of treatment on Heart Rate

HR	Mean	SD	N	mean difference	paired 't'	p
0 min	80.3	6.2	53	-	-	-
15 min	70.0	7.3	53	10.34	12.66**	0.000
30 min	64.8	7.3	53	15.57	18.65**	0.000
45 min	58.1	8.2	53	22.19	19.57**	0.000
60 min	54.8	8.4	53	25.49	21.07**	0.000
1 hr 15 min	52.6	8.2	53	27.74	22.05**	0.000
1hr 30 min	53.9	6.8	53	26.40	22.98**	0.000
1 hr 45 min	56.5	6.8	53	23.79	19.90**	0.000
2 hr	57.1	6.4	53	23.23	20.09**	0.000
2 hr 15 min	58.7	6.2	53	21.60	19.04**	0.000
2 hr 30 min	60.9	4.8	53	19.40	18.35**	0.000
2 hr 45 min	63.0	5.0	53	17.34	15.69**	0.000
3 hr	61.0	4.7	53	19.30	18.16**	0.000
3 hr 15 min	63.7	5.3	43	16.79	14.01**	0.000
3 hr 30 min	64.3	4.4	36	16.31	13.10**	0.000
3 hr 45 min	64.3	4.6	21	15.67	8.99**	0.000
4 hr	65.7	3.9	13	14.00	6.48**	0.000

**: - Significant at 0.01 level

The analysis shows a significant (significant even at 0.01 level) decrease in heart rate when compared to baseline i.e., before administration of drug. But never to an extent has that had which endangered life of patient. Least mean heart rate is 52.6 at 1 hour 15 minutes after administration of drug

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Table Effectiveness of treatment on SBP

SBP	Mean	SD	N	mean difference	paired 't'	p
0 min	114.1	12.1	53	-	-	-
15 min	107.1	11.8	53	7.06	10.11**	0.000
30 min	107.1	10.6	53	7.04	7.05**	0.000
45 min	106.6	9.3	53	7.53	8.03**	0.000
60 min	107.9	8.2	53	6.21	5.67**	0.000
1 hr 15 min	108.5	7.8	53	5.66	4.92**	0.000
1hr 30 min	111.5	8.5	53	2.66	2.17*	0.035
1 hr 45 min	112.2	8.7	53	1.87	1.48	0.144
2 hr	111.8	9.0	53	2.32	1.78	0.082
2 hr 15 min	110.8	9.9	53	3.36	2.90**	0.005
2 hr 30 min	110.7	8.1	53	3.40	2.60*	0.012
2 hr 45 min	111.6	8.1	53	2.55	2.01	0.050
3 hr	112.0	9.0	53	2.09	1.77	0.082
3 hr 15 min	110.9	9.4	40	4.90	4.19**	0.000
3 hr 30 min	111.3	10.5	34	4.26	3.61**	0.001
3 hr 45 min	113.0	11.0	21	3.95	3.27**	0.004
4 hr	113.2	12.5	13	2.69	1.68	0.118

**: - Significant at 0.01 level, *: - Significant at 0.05 level

After an initial significant decrease, there is rise in Systolic blood pressure. The least mean value is 106.6 at 45 minutes. At 1 hour 45 minutes and at 2 hours, blood pressure raised and there is no significant difference from baseline. There is no significant rise in blood pressure which needed to be controlled by other agents.

Figure showing Effectiveness of treatment on SBP

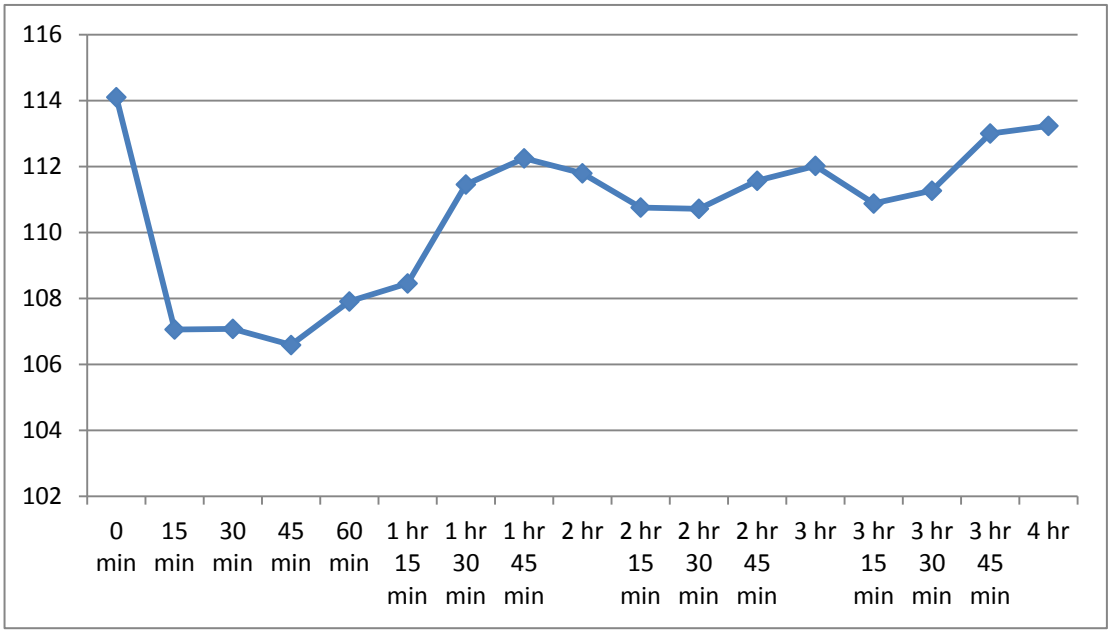

Figure showing Effectiveness of treatment on DBP

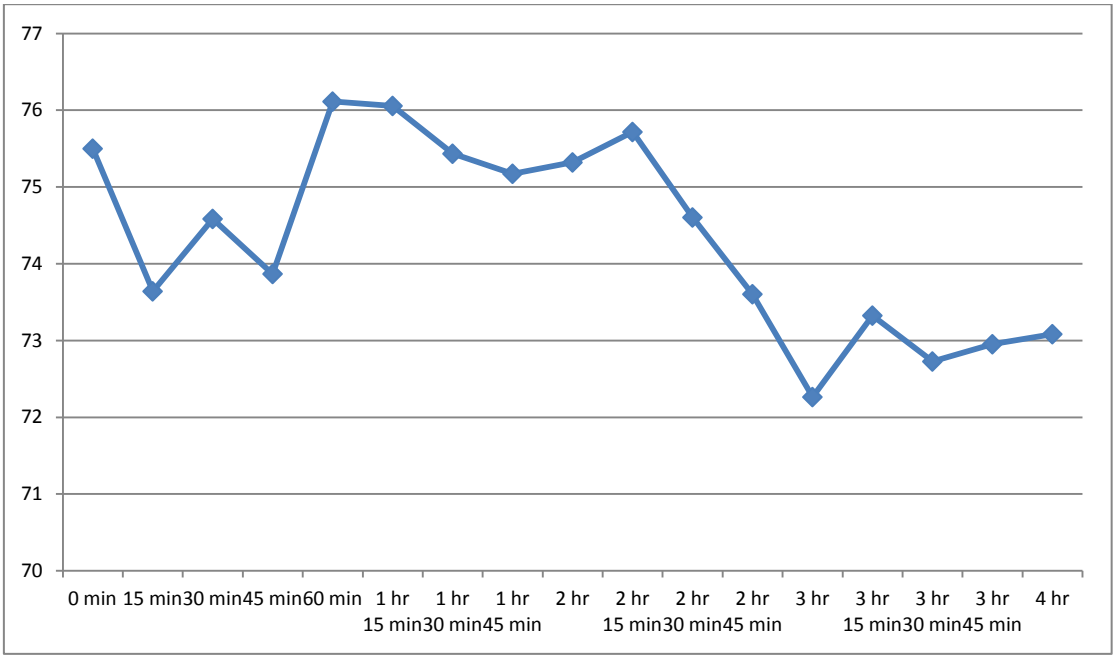

Table Effectiveness of treatment on DBP

DBP	Mean	SD	N	mean difference	paired 't'	p
0 min	75.5	6.3	53	-	-	-
15 min	73.6	6.0	53	1.89	5.67**	0.000
30 min	74.6	6.0	53	0.94	2.69**	0.010
45 min	73.9	5.6	53	1.66	4.32**	0.000
60 min	76.1	5.4	53	-0.58	1.71	0.092
1 hr 15 min	76.1	5.6	53	-0.53	1.42	0.161
1hr 30 min	75.4	5.7	53	0.09	0.20	0.838
1 hr 45 min	75.2	5.8	52	0.46	0.96	0.344
2 hr	75.3	5.4	53	0.21	0.38	0.709
2 hr 15 min	75.7	5.8	53	-0.19	0.35	0.728
2 hr 30 min	74.6	5.5	53	0.92	1.73	0.089
2 hr 45 min	73.6	5.9	53	1.92	3.39**	0.001
3 hr	72.3	5.8	53	3.26	6.58**	0.000
3 hr 15 min	73.3	5.9	40	3.58	5.61**	0.000
3 hr 30 min	72.7	6.1	33	3.82	4.97**	0.000
3 hr 45 min	73.0	5.4	21	3.57	4.15**	0.000
4 hr	73.1	7.2	12	2.58	2.00	0.071

**: - Significant at 0.01 levels

There is no significant alteration in diastolic blood pressure especially during the procedure. The significant decrease is seen before creation of pneumo-peritoneum and after release of pneumo peritoneum. Maximum mean rise in diastolic blood pressure in 75.7 mm Hg and maximum fall in diastolic blood pressure is 72.3 mmHg

DISCUSSION

In the present study, we were observing patients who were given Dexmedetomidine and their response to the stress events during surgery. Multiple points of time the chance of stress are high like during intubation, during pneumo-peritoneum, during head down position. The result showed that the stress response were minimal when Dexmedetomidine was given as bolus and then continued as infusion. Even in post-operative period, after a smooth extubation possible with Dexmedetomidine, patient remained calm for another one hour and was then shifted to post-operative ward.

When compared to baseline there was significant decrease in heart rate. But never the heart rate has fallen to dangerous level. There were no increases in heart rate after administration of Dexmedetomidine without use of additional agents for control the stress response. Maximum fall in mean heart rate is 52.6 and maximum after 1 hour 15 minutes of surgery. Fall in heart rate is seen in other studies like with studies of D.P Bhattachharjee, Yogesh Chauhan. [32][38] After that heart rate increased, but never to extend it reached baseline. Though there is bradycardia not to rate less than 40 beats per minute, also it was very gradual. Bradycardia never occurred worrisome. If heart rate falls before 40 beats per min, it easily responded to inj. Atropine 0.6 mg. This reversibility with atropine is also studied in article by Carollo DS [37]

Systolic blood pressure showed a fall generally rather than increase which is usually seen in laparoscopic surgeries. Response to patients to Dexmedetomidine depended on pre health status of patient. Some were at pre hypertensive level, their response were unpredictable. One patient had hypertensive crisis after bolus dose as described in books with Dexmedetomidine. But overall statistical analysis showed maximum fall in blood pressure to a mean value of 106.6 by 45 minutes after start of study approximately correlating to creation of pneumo-peritoneum. It further increased after head down position, but reached to base line only at end of surgery.

At higher dose of Dexmedetomidine, it produces a hypertensive action caused by activation of alpha 2 adreno-receptor located on vascular smooth muscle cells. Its more seen with rapid injection of Dexmedetomidine. [33]

Diastolic blood pressure had a fall initially. But after creation of pneumo-peritoneum which corresponded to 45 minutes of surgery there was increase. But there was never a significant rise in diastolic blood pressure. Fall in mean blood pressure was maximum of 73.9 at 45 minutes, then gradual rise to maximum mean diastolic blood pressure of 76.1 at 1 hour 15 minutes. Dexmedetomidine controlled the rise in diastolic blood pressure after pneumo-peritoneum creation. Dexmedetomidine did not cause much fall in diastolic blood pressure.

Finally requirement for anti-hypertensive in the intra operative period was none. This provides a great advantage for us to use Dexmedetomidine in cardiovascular unstable patients.

When observed post-operative period patients were stable. There were no significant rises in blood pressure because of pain or significant fall in blood pressure due to sedation. Patient did not have nausea or vomiting. Gynecological surgeries pose serious post-operative nausea and vomiting. Anti-emetic effect of Dexmedetomidine was achieved with the dosage which was used in the study.

Researches were there showing infusion of Dexmedetomidine helpful in alleviating post-operative shivering, nausea and vomiting in gynecological laparoscopic surgeries. [34][35][36]

Analgesia was achieved with injection diclofenac 75mg at the end of surgery. Requirement of opioid was not there for analgesia. Patient remained calm. Length of post of anaesthesia care unit was not increased due to administration of Dexmedetomidine.

LIMITATION OF STUDY

1) It was not a case control study to compare effect with other agents. Limitation of observational study was definitely present.
2) Study did not evaluate the decrease in use of other agents to reduce stress and pain. Though during study it was clear that use of inhalational agents, opioids was comparatively less but quantification of data was not done.
3) Entropy was not used to measure level of consciousness. As use of other agents was less, there was a chance of awareness. Patients were comfortable in post op period too was only measure to know there was adequate depth of study.

4) Study was limited to ASA PS 1 and ASA PS 2 patients, though Dexmedetomidine decreased work load on heart novelty of drug did not permit use in ASA PS 3and ASA PS 4 patients

SUMMARY AND CONCLUSION

Dexmedetomidine used as premedication and during intra operative period definitely decreased stress response associated with surgery, intubation, and pneumo-peritoneum creation and after head down position.

Patient remained calm and had pain relief minimum 1 hour post-operative period which was added advantage of Dexmedetomidine. Without over sedation and respiratory depression of other agents

According to this study, Dexmedetomidine provides a definite advantage over other agents commonly used for high stress surgeries like gynecological laparoscopic surgeries

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APPENDIX
PROFORMA

SERIAL NUMBER
NAME :
AGE:
ASA PS STATUS:
IN PATIENT NUMBER:
SURGICAL PROCEDURE:

	HEART RATE	SYSTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE
0 MIN (BASELINE VALUE)			
15 MIN (PRE INDUCTION VALUES)			
30 MIN (POST INDUCTION VALUES)			
45 MIN			
60 MIN (AFTER PNUEMOPERITONEUM)			
1 HOUR 15 MIN (AFTER HEAD DOWN)			
1 HOUR 30 MIN			
1 HOUR 45 MIN			
2 HOURS			
2 HOURS 15 MIN			
2 HOURS 30 MIN			
2 HOURS 45 MIN			
3 HOUR			
3 HOURS 15 MIN (BEFORE EXTUBATION)			
3 HOURS 30 MIN (AFTER EXTUBATION)			
3HOURS 45 MIN			
4 HOURS			

CONSENT FORM

I have been informed that this is a study conducted by Dr. Sherin Sara Roy as a part of her P.G curriculum. It has been explained in detail to
me regarding the implications of participating in the study as well as the possible complications that can occur during or after the study. I have been assured that all my medical records will be kept confidential and no personal references will be made in the study. I have also been assured that no cash or other equivalents have to be incurred for enrolment or discontinuation from the study. The results obtained from the study may be used for scientific publications. All doubts regarding the study have been cleared by the doctor concerned. I also am aware that I can withdraw from the study at any time and that my withdrawal would not affect the treatment or care provided to me. Being aware of the implications of the study, I consent to enroll myself in the study.

Date:
Place :

Name of the patient:
Address:

Signature:
Name of Witness:
Address:

Signature:

Dr. Sherin Sara Roy
9037663880
Signature: