"EFFECTIVENESS OF RAMOSETRON FOR PREVENTION OF SHIVERING IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES UNDER SPINAL ANAESTHESIA – ONE YEAR HOSPITAL BASED, DOUBLE BLINDED RANDOMIZED CLINICAL TRIAL."

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ENDORSEMENT

This is to certify that the dissertation entitled **"EFFECTIVENESS OF RAMOSETRON FOR PREVENTION OF SHIVERING IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES UNDER SPINAL ANAESTHESIA – ONE YEAR HOSPITAL BASED, DOUBLE BLINDED RANDOMIZED CLINICAL TRIAL."** is a bonafide research work done by **(REG NO.BA0119010)**, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belagavi – 590 010.

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LIST OF ABBREVIATIONS USED

ASA	-	American society of Anaesthesiologists
SAB	-	Subarachnoid Block
SA	-	Spinal anaesthesia
GA	-	General anaesthesia
PAS	-	Post-anaesthesia shivering
PSS	-	Post spinal shivering
POS	-	Perioperative shivering
NS	-	Normal saline
PONV	-	Postoperative nausea and vomiting
Inj.	-	Injection
i.v	-	Intravenous
Mins	-	Minutes
Hrs	-	Hours
CVS	-	Cardiovascular system
RS	-	Respiratory system
GIT	-	Gastrointestinal tract
CNS	-	Central Nervous System
Hb	-	Haemoglobin
HR	-	Heart rate
RR	-	Respiratory rate
PR	-	Pulse rate
BP	-	Blood pressure
ECG	-	Electrocardiogram
CXR	-	Chest X-ray
MAP	-	Mean Arterial Pressure
MAC	-	Minimum Alveolar Concentration
FBS	-	Fasting blood sugar
CSF	-	Cerebrospinal fluid
5-HT3	-	5-hydroxytryptamine 3
5-HT3R	-	5-hydroxytryptamine 3 Receptor
RCT	-	Randomized control trial

α	-	Alpha
β	-	Beta
SPO_2	-	Saturation percentage of oxygen
MPG	-	Mallampati Grading
T	-	Time
EMG	-	Electromyogram
CO_2	-	Carbondioxide
O_2	-	Oxygen
N_2O	-	Nitrous Oxide
BMI	-	Body mass index
BMR	-	Basal metabolic rate
NMDA	-	N-Methyl D-Aspartic acid
GABA	-	Gamma Amminobutyric Acid
AUC	-	Area under Curve
MAO-I	-	Monoamine oxidase Inhibitor
µg / mcg	-	Micrograms
mg	-	Milligrams
Kg	-	Kilogram
ml	-	Milliliters
&	-	And

ABSTRACT

Background and Aim:

Perioperative shivering (POS) is a commonly observed cumbersome problem in patients undergoing surgeries under spinal anaesthesia (SA). Various non-pharmacological and pharmacological approaches have been tried and tested to prevent and control shivering. Shivering has tremendous deleterious effects on the body metabolism. Numerous studies supported the anti-shivering property of 5-HT3 receptor (5-HT3R) antagonists, even though not a single study has shown substantial results. This study intends to determine the efficacy of ramosetron (a 5-HT3 receptor antagonist) 0.3mg intravenously (i.v) when compared with 0.9% normal saline(NS) to prevent post spinal shivering (PSS) during planned infraumbilical surgeries.

Method:

This study consists of 70 patients of ASA I/ II, who were posted for elective infraumbilical surgeries under subarachnoid block (SAB). These patients have been randomized into two groups, where Group A received 0.3mg ramosetron i.v diluted to 4ml immediately after induction of SAB and Group B received 0.9%NS (4ml) i.v. Incidence of shivering, intensity of shivering at any given time on a grading scale (0-4) by Crossley & Mahajan was observed and core body temperature was measured every 30 minutes (mins). Any shivering was treated with Inj. Tramadol 1mg/kg.

Results:

The data obtained on comparing the shivering incidence at any given point of time was statistically significant (P = 0.001).

Conclusion:

Ramosetron 0.3 mg is an efficacious drug in the prevention of PSS among patients who have been posted to undergo elective infraumbilical surgeries. Furthermore, no significant side effects were observed with the administration of ramosetron 0.3mg i.v.

Keywords: post-spinal shivering, ramosetron, thermoregulation

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INTRODUCTION

The normal human body temperature is maintained between a narrow range of 97°F to 99°F, which is necessary for normal physiologic and metabolic functions. Shivering is a physiological response of body to environmental changes in the temperature. It has an incidence of 60% following general anaesthesia and upto 33% following regional anaesthesia.[1]

Various lower abdominal and lower limb surgeries are commonly carried under spinal anaesthesia. Intraoperative shivering is frequently observed in patients undergoing surgery under spinal anaesthesia. The etiology of shivering is not clear, however it is believed to involve a combination of mechanisms, such as impairment of the thermoregulatory threshold, a reduction in the core body temperature, alterations in the body heat distribution and the result of injecting cool fluids in the body, any or all of which may lead to a decrease in the threshold for vasoconstriction and shivering.[2]

Shivering causes considerable discomfort to the patient. In addition, it also increases oxygen consumption upto 300 times. This may be tolerated in ASA grade I and II patients but may be particularly deleterious in patients with borderline cardiac function. Severe shivering leads to difficulty in the monitoring of vitals such as pulse oximetry, BP and ECG during the period of sympathetic sensory blockade.

Typically, many drugs such as ketamine, meperidine, tramadol and clonidine are used for the treatment of intraoperative shivering rather than preventing it. These medications are associated with different adverse effects such as nausea and vomiting, sedation, hypotension and bradycardia, thus restricting the use of these drugs.[3]

Serotonin 5HT3 receptors are located in brain and spinal cord.[4] 5HT3 antagonists act by inhibiting the reuptake of serotonin at pre-optic region of the anterior hypothalamus, which exerts its influence on both the heat production & heat loss thus exerting their anti-shivering effect.[5]

Recently, the 5HT3 antagonists, ondansetron and granisetron have been tested for prevention of post anaesthetic shivering (PAS). These studies have yielded good results.[6,1]

Ramosetron is among the newest 5HT3R antagonist. It is widely used as an antiemetic agent. It is reported that out of all the available 5HT3R antagonists, ramosetron shows the most sustained and potent antagonistic activity towards the serotonin receptors[7,8] and prolonged duration of action compared to ondansetron.

A thorough literature search did not reveal any study determining the effectiveness of ramosetron as an antishivering agent in patients undergoing infraumbilical surgeries under spinal anaesthesia in the indian population.

The objective of this study is to evaluate the preventive effect of a single i.v dose of ramosetron (0.3mg), when compared with 0.9% NS for the prevention of postspinal shivering (PSS).

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

To determine the efficacy of ramosetron for the prevention of shivering following spinal anaesthesia.

SECONDARY OBJECTIVE:

To study the side effects of ramosetron if any.

REVIEW OF LITERATURE

In 1885, James Leonard Corning, a neurologist from New York was the first to administer spinal analgesia. In 1898, August 15, August Bier first performed spinal anaesthesia with cocaine on a healthy male along with his assistant August Hidebrandt. However, it is assosciated with various complications such as hypotension, hypothermia, post dural puncture headache, transient neurological symptoms, nausea and vomiting widely related to the procedure or drugs used during the procedure. Since then the technique underwent various modifications in order to decrease the incidence and management of these complications. However, shivering is one such frequent complication which troubles both the anaesthesiologist as well as the patient.

In 1868, Wunderlich, the German physician emphasized on the clinical usefulness of recording body temperature. Various methods for temperature monitoring have been described to detect the occurrence of shivering during anaesthesia. Both non pharmacological methods and pharmacological drugs are being used to treat shivering. Despite the available knowledge, there are many voids in regards to management clinically.

In spinal anaesthesia there is a major conduction block which significantly impairs the thermoregulation by inhibiting the shivering and vasomotor responses and heat redistribution from the core body to the peripheral tissues.[9] This predisposes the patients to develop hypothermia while undergoing regional anaesthesia, which may be as equally common & severe as when the patient undergoes general anaesthesia.[10,11] Since regular monitoring of the core body temperature is not usually practiced, hypothermia goes unrecognised in substantial amount of patients.[12] Peri-operative hypothermia is usually related with adverse consequences such as discomfort, shivering, bleeding & infection. To

avoid this, it is necessary to identify the prognostic clinical factors of core hypothermia, which will help in monitoring and controlling the core temperature of the patients. There are various studies which have acknowledged the influential factors of hypothermia in patients undergoing general anaesthesia such as older age, lower ambient temperatures & reduced lean body mass. However, in spinal anaesthesia the predictors are different for hypothermia as the hypothalamus which is the centre for thermoregulatory control is not being affected directly & the changes that occur in the vasomotor tone also follow a dissimilar pattern.[13]

In one study conducted by Frank and his colleagues on predictors of hypothermia during spinal anaesthesia, 44 patients who underwent radical retropubic prostatectomy have been signed up. 18-22mg 0.75% bupivacaine admixed with 20 mcg fentanyl was given as a lumbar intrathecal injection. Only intravenous fluid warming was used as an active warming measure. It was noted that the core body temperature reduces quickly to greater than 1°C lower than baseline in the initial 45 minutes. Surgery duration, operating room temperature, BMI & body fat percentage could not substantially predict hypothermia. However, higher level of SA & increased age were substantial predictors of decreased core body temperature by univariate and multivariate tests. Higher levels of SA is acknowledged to reduce the threshold for shivering of core body temperature. For an increase in each higher level of block, a reduction of 0.15°C in core body temperature was noted. For every year of increased age there was 0.03°C reduction in the core body temperature.[13]

In 2003 Dr. Pradeep K Bhattacharya reviewed physiology of post anaesthetic shivering (PAS), thermoregulatory mechanisms and several preventive measures such as the pharmacological as well as the non-pharmacological managements. In homeothermic species, the thermoregulatory defences are coordinated to balance the core body

temperature within a narrow range. Since shivering is seen as a common side effect for both general and regional anaesthesia, it causes discomfort to the patient & further leads to several deleterious consequences. Hence, appropriate steps are needed to prevent & treat shivering, the utmost effective measures being forced air warming & fluid warming. The pharmacological substances for treating it are tramadol, morphine, pethidine, physostigmine, fentanyl & nefopam etc. [14]

Measurement of core body temperature is done by invasive methods like pulmonary artery catheter and is not commonly used. The non-invasive techniques such as the axillary thermometry is reliable and correlates with the rectal temperature. A study was conducted among 174 patients in Sudan, 2012 to check the accuracy of tympanic temperature measurement with the help of an infrared tympanic thermometer, which was found to be reliable and accurate to axillary mercury thermometry. Thus, tympanic thermometry can be used in clinical practice due to its ease of use and in conditions where it is important to obtain the reading immediately.[15]

Many drugs which were compared for the treatment and prevention of POS are also associated with various side effects. Thus, even today many studies are being done to find a drug which can be used effectively in the management of shivering.

The efficacy of ondansetron which is known for the treatment of postoperative nausea & vomiting (PONV) has been investigated on the intraoperative temperatures of the core, periphery and PAS. 82 patients between 18-60years undergoing general, orthopaedic or urological procedures were randomized to 3 groups in this double blinded and placebo controlled study. Group O4 with sample size of 27 received 4mg of ondansetron i.v, Group O8 with sample size of 27 received 8mg ondansetron i.v and Group C with sample size of 28 received normal saline i.v immediately prior to induction of anaesthesia. The core

tympanic temperature & temperature of the middle finger tip were recorded. Induction of general anaesthesia (GA) was proceeded with Inj. fentanyl 1 mcg/kg i.v, Inj. propofol 2 - 2.5 mg/kg i.v & maintained 1 MAC isoflurane in 70% N_2O/O_2. The rate of shivering was clinically documented by the recovery nursing staff, who did not have knowledge of the group assigned to the individual. Incidence of PAS is 16 out of 28 patients (57%) in Group C, compared to 9 out of 27 patients (33%) in the Group O4 (P 5 0.13) and 4 out of 27 patients (15%) in the Group O8 (P 5 0.003). In each group, there was a decrease in core body temperature and increase in peripheral temperature, but at any given time there was not much significant difference among the groups. Hence, they concluded that 8mg of ondansetron when given i.v during the anaesthetic induction helps in preventing PAS without disturbing the core-to-peripheral heat redistribution. This proposes that the serotonergic pathways play an important role in the regulation of PAS.[16]

Another double blinded study was done to evaluate the effect of ondansetron in prevention of post spinal shivering in 80 parturients undergoing elective caesarean section. Ondansetron 8mg i.v diluted to 4ml has been given to 40 parturients whereas the remaining 40 parturients received the equal volume of 0.9%NS. PSS & maximum grade of shivering at any given time was noted on a scale (0-4) & the total dose of meperidine needed to treat shivering at a score more than or equal to 3 was calculated. Total dose of ephedrine that is required to treat hypotension & maternal MAP was assessed pre-spinal, post spinal, after giving position and baby delivery. On comparison of the ondansetron and saline group, it was documented that the shivering rate, maximum shivering, the total dose of meperidine & incidence of nausea was decreased in the former group.[17]

In another double blinded study of 60 ASA 1 and 2 patients in the age group of 20-50 yrs posted for lower abdominal elective surgeries under SA, granisetron versus pethidine has been studied for the prevention of perioperative shivering. 40 mcg/kg Granisetron i.v &

0.4 mg/kg pethidine i.v have been administered to the patients of respective groups. Perioperative vitals & core body temperature were observed & shivering was evaluated using the 5-item scale every 15 mins for up to 6 hrs. It was observed that 6 patients in either group had shivering. The mean temperature where the patient developed shivering was at 36.31°C & 35.85°C. The mean onset time of shivering was at 95mins and 65mins in granisetron group and pethidine group respectively. Hence, it was concluded that prophylactic 40 µg/kg granisetron i.v is as effective as 0.4 mg/kg pethidine i.v in preventing shivering post SA & also decreases the requirement of anti-emetics.[1]

In 2014, another study was perfomed which contradicted the efficacy of granisetron as a prophylactic medication against shivering in parturients posted for elective caesarean section under spinal anaesthesia. The study enrolled 117 ASA grade I or II parturient females who were randomized into 2 groups consisting 58 parturients in each; Group G received 3mg granisetron in 3ml i.v & group P received 3ml of normal saline i.v prior to the induction of spinal anaesthesia with 10 mg heavy 0.5% bupivacaine and 15 µg fentanyl. Intake of rescue medication, incidence of maternal vomiting for 12hours postoperatively, interference with neonatal holding and APGAR score was noted. Interference of shivering with monitoring of the patient and also tympanic membrane temperature was noted. There was not much significant statistical difference in the percentage of shivering & shivering score among parturients of either groups, with a P value more than 0.05. No statistical difference was noted in regards with the intake of rescue medication (P = 0.086), neonatal holding (P = 0.653) & interference with monitoring (P = 0.653). Additionally, tympanic membrane temperature (P = 0.48) & 1 minute APGAR score (P = 0.09) didn't show any significant difference statistically. However, granisetron significantly decreased the incidence of nausea & vomiting to 10.3% & 27.1% in Group G & Group P respectively (P = 0.036).[18]

A single blinded study had been performed to compare the efficacy & tolerability of ramosetron versus granisetron over a period of 24 hours following chemotherapy with cisplatin. 194 patients were randomized to receive either 0.3mg ramosetron i.v or 3mg granisetron i.v. Ramosetron had a longer no-vomiting rate with nil significant variation in the number of acute vomitings or the severity of nausea amongst the 2 groups. There was a notably higher incidence of dull headache in the granisetron group. Apart from it, there wasn't much significant statistical difference among the two groups. They appear to be equally efficacious and tolerable, however the effects of ramosetron in the prevention of vomiting lasted longer. The inhibitory outcome of ramosetron on 5-HT3R binding of the labelled 5-HT is described to be more effective than the binding of ondansetron or granisetron.[19]

Incidence of shivering with perioperative ramosetron in 80 parturients undergoing elective caesarean section under spinal anaesthesia was studied. Amongst them, 40 parturients received ramosetron 0.3mg i.v whereas the other 40 parturients received 0.9% NS in equal volumes of 4ml immediately prior to induction of spinal anaesthesia. Blinding of the investigator to the treatment group was ensured as he graded POS in a scale of 0-4. Significant statistical data had been obtained while comparing the shivering incidence & maximum grade of shivering at any given time ($P = 0.001$) between both the groups. Ramosetron group had an added benefit in preventing the maternal nausea along with better haemodynamic parameters.[3]

Ramosetron 0.3mg i.v was evaluated for its effects on prevention of shivering after spinal anaesthesia in patients who underwent knee arthroscopy. 52 ASA 1 and 2 patients who were involved in the study, were equally divided into 2 groups: ramosetron & placebo. The drug at test in each group was given immediately prior to induction of SA after double blinding. They found that in ramosetron group, 2 patients experienced shivering in contrast

to nine patients from the placebo group (P = 0.038, odds ratio = 6.14, 95% C.I. = 1.08-65.5). The difference in the core body temperature among the groups wasn't very significant. They concluded that ramosetron when compared to the control group is an effective method to prevent shivering during SA.[20]

Another systematic review and meta-analysis studied 13 RCTs consisting of 1139 patients. The overall incidence of POS was significantly lesser in 5-HT3R antagonist group (RR 0.31; 95%CI 0.26 to 0.38; p <0.010). Subgroup analysis for various types of 5-HT3R antagonists & timing of administration showed similar results. Likewise, patients showed a lower incidence of PONV after the administration of 5-HT3R antagonists. Statistically no significant difference has been observed in the drug-related adverse effects.[21]

A meta-analysis has been conducted to assess the efficacy and the safety of 5-HT3R antagonists on the prevention of POS. Eligible randomized controlled trials were identified with the help of a thorough search in all the relevant databases through January 2016. Incidence of POS was taken as the primary outcome & the incidence of safety-related outcomes such as postoperative nausea and vomiting (PONV), hypotension & bradycardia were considered as the secondary outcome. 16 studies which included 1,126 patients were involved in meta-analysis. In the conventional meta-analysis, when compared with the control group, 5-HT3R antagonists significantly reduced the incidence of shivering when given i.v & prevents POS in adults undergoing general and neuraxial anaesthesia. However, RCT of higher quality with larger sample size is needed to come to any conclusion regarding the efficacy of 5HT3R antagonists on prevention of POS.[22]

Considering the high probability of effectiveness of ramosetron which is a highly potent 5HT3R antagonist in the prevention of shivering, the current study was undertaken to

determine the efficacy of 0.3mg of ramosetron given immediately post administration of spinal anaesthesia.

BASIC SCIENCES

SUBARACHNOID BLOCK

The subarachnoid block (SAB) is a type of regional anaesthesia which involves the injection of the local anaesthetics into the subarachnoid space. It exerts its action via spinal nerve roots & the dorsal ganglion to produce sensory analgesia, sympathetic blockade and motor blockade.

Indications[24,29]:

- Caesarean sections
- Surgeries which involve the lower half of body
    - Lower abdomen
    - Lower extremity
    - Perineum
- Diagnostic and therapeutic procedures below the level of diaphragm.

Contraindications[24,29]:

- Absolute
    - Patient refusal
    - Skin infection at the injection site
    - Raised intracranial pressure
    - Coagulopathies
    - Severe hypovolemia
    - Sepsis
    - Severe Aortic valve or Mitral valve stenosis

- Relative
    - Spinal deformities
    - Pre-existing neurological deficits
    - Uncooperative patient
    - Demyelinating lesions

ANATOMY [23,25]

To perform the subarachnoid block, a thorough knowledge about the anatomy of spinal canal, vertebral column and spinal nerve is essential.

Vertebral column

It gives structural support and protection to the spinal cord.

There are

- 7 Cervical vertebra
- 12 Thoracic vertebra
- 5 Lumbar
- 5 Sacral
- 4 Coccyx (fused)

Parts of the vertebra

- Anteriorly - Body
- Posteriorly - Two pedicles
- Two lamellae - connect the pedicles
- Lamella - give rise to the spinous process posteriorly and transverse process laterally.

Vertebral pedicles are notched. These opposite notches fuse to form a foramen out of which Spinal nerves comes out. At the lamellar junction, articular processes (superior and inferior) arise.

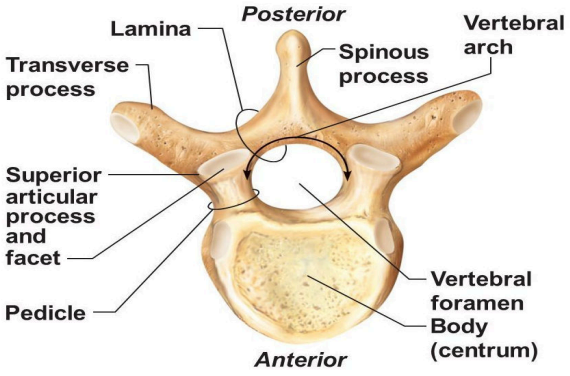


Fig 1 : Anatomy of Vertebra

Ligaments

They support the vertebral body.

Supraspinous ligament - A thick, Strong and fibrous band extending from the seventh cervical (C7) vertebra to sacrum. From C7 it continues as ligament nuchae and attaches to the occipital protuberance.

Interspinous ligament - A thin, fibrous structure which extends from the apex and upper surface of the lower spine towards the root and inferior surface of the next higher vertebrae.

Ligamentum flavum - Extends vertically from the anterior surface of the upper lamina to the inferior surface and inferiorly to the antero-superior surface of lower lamina. On exiting the intervertebral foramen, the ligament divides into right and left halves as they fuse in the midline.

Curvatures of the spine

- Cervical curve - Convex anteriorly
- Thoracic curve - Convex posteriorly
- Lumbar curve - Convex anteriorly
- Sacrococcygeal - Convex posteriorly

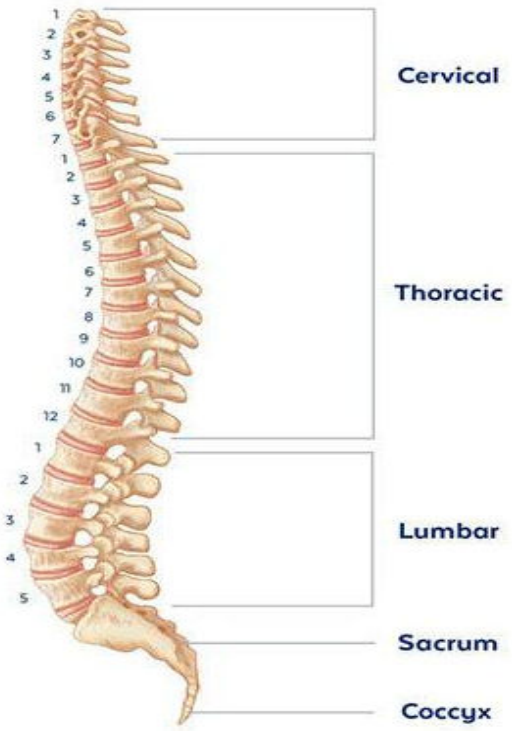


Fig 2: Curvatures of spine

Meninges[23,24]

Spinal canal meninges comprises of 3 membranes which are in sequence with the cranial meninges namely;

- Pia mater
- Arachnoid mater
- Dura mater

Subarachnoid space

It is the space between the arachnoid mater and pia mater. It contains CSF. It communicates with the space around the blood vessels of pia mater which is called the Virchow Robin Space. This space consists of blood vessels, nerve roots and CSF.

Subdural space

The space between arachnoid and dura mater is called as subdural space. It consists of a thin serous fluid which separates the two layers. The traumatic brain injury is usually presented as subdural haematoma.

Epidural space

It is a space between the periostium of the vertebral canal and the dura mater. It extends from the foramen magnum to sacrococcygeal ligament. It consists of fat, loose areolar tissue, spinal arteries and batson's plexus and nerve roots. Epidural block is a common anaesthesia technique used for surgeries involving lower half of the body.

Cerebrospinal fluid[29]

CSF is a clear fluid covering the brain and subarachnoid space. It is formed by the secretion and ultra filtration from the choroid plexus. It gets eliminated be being absorbed by the arachnoid villi. It flows from the lateral ventricle to 3rd ventricle and it enters 4th ventricle via the foramen of Monro. It reaches the subarachnoid space via the foramen of Luschka and Magendie. The total volume of CSF in adult is about 150 ml of which 25ml is present in the ventricle and 125ml in the subarachnoid space. 400- 600ml of CSF is produced every day.

Composition of CSF

- Specific gravity- 1.003-1.009
- pH- 7.27 - 7.37
- pCO_2- 48 mm Hg
- Na- 135-145mEq/L
- Cl- 15-20mEq/L
- HCO_3- 23mEq/L
- Proteins – 23-38mg/dl
- Sugar- 50-80mg/dl

Spinal cord

It is a thin, long structure which consists of nervous tissue. It extends from the medulla oblongata to the lumbar vertebral column. It is divided into gray matter and white matter. In children, spinal cord terminates at lower border of L3 vertebra whereas in adult, it ends between L1 and L2 vertebra. There are thirty one pairs of spinal nerves. After the L1 vertebra, the spinal cord terminates as a fibrous extension called as the filum terminale.

Spinal nerves

There are:

8 cervical nerves

12 thoracic nerves

5 Lumbar nerves

5 Sacral nerves

1coccygeal nerve

Each nerve is formed by a combination of anterior & posterior spinal roots. Each spinal nerve passes via a pair of intervertebral foramina.

Each pair of spinal nerve divides into an anterior motor root and posterior sensory root.

Structures pierced during subarachnoid block

- Skin
- Subcutaneous tissue
- Supraspinous ligament
- Interspinous ligament
- Ligamentum flavum
- Dura mater

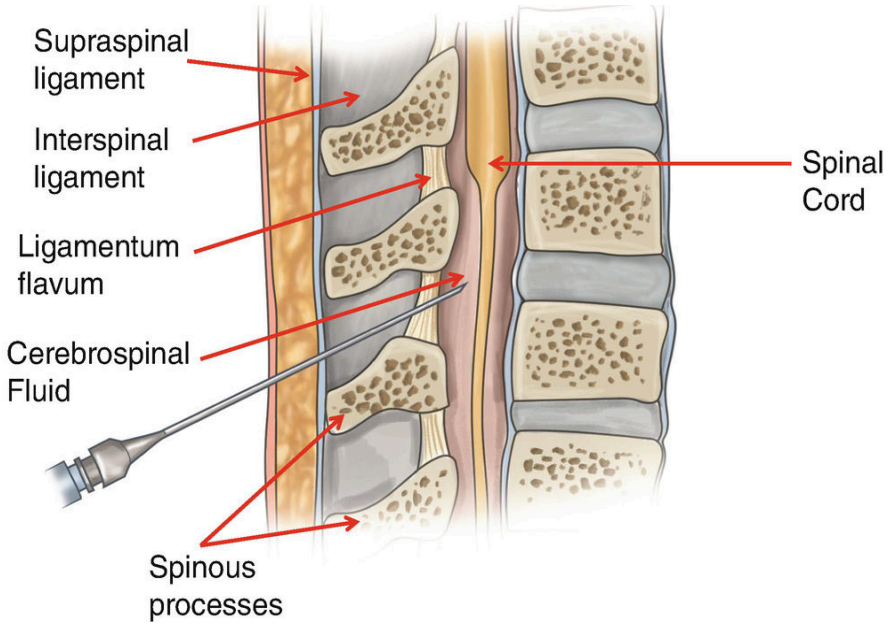


Fig 3: Spinal anaesthesia

THERMOREGULATION

The normal body temperature by homeotherms is maintained within a narrow range of 36.7^0C to 37.5^0C by a balance between heat production and heat dissipation.

The three components which are involved in the process of thermoregulation to maintain core body temperature include [26,27,28]

1. Afferent thermoreceptors

2. Central regulation

3. Efferent responses

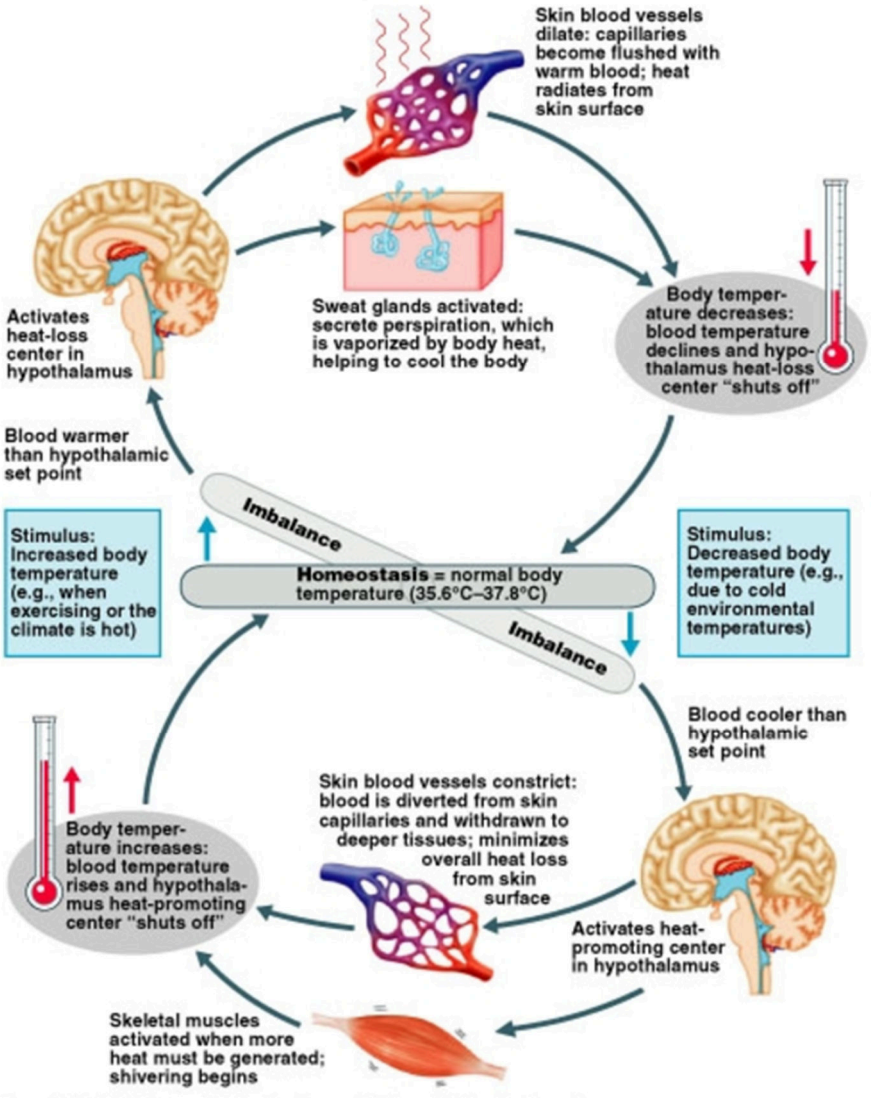


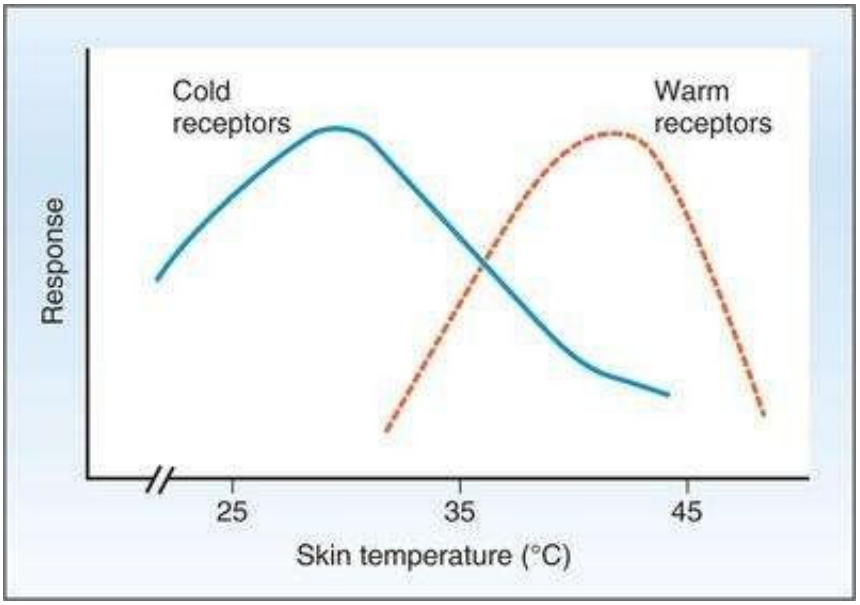
Figure 4: Physiology of thermoregulation

AFFERENT THERMORECEPTORS:

Thermoreceptors are non-specialized sensory receptors or exteroceptors which exist as free nerve endings. They obtain absolute and relative changes in the environmental and body temperature within the innocuous range. They are widely distributed throughout the body such as skin surface, deep abdominal and thoracic tissues, and few areas of CNS including spinal cord and hypothalamus.

A-delta receptors carrying cold sensations and C fibers which transmit warm signals, discharge signals maximally at 25°C to 30°C and 45°C to 50°C respectively. The thermal inputs from skin and deep tissue are integrated at various levels in the spinal cord and the brainstem, where considerable modulation of inputs occur. Thermal sensations are transmitted by lateral spinothalamic tracts and tracts in the anterior spinal cord of which major transmission occurs by anterior spinothalamic tract. In brainstem, areas like raphe magnus nucleus and sub coeruleus function as a relay station in the transmission of thermal sensations.

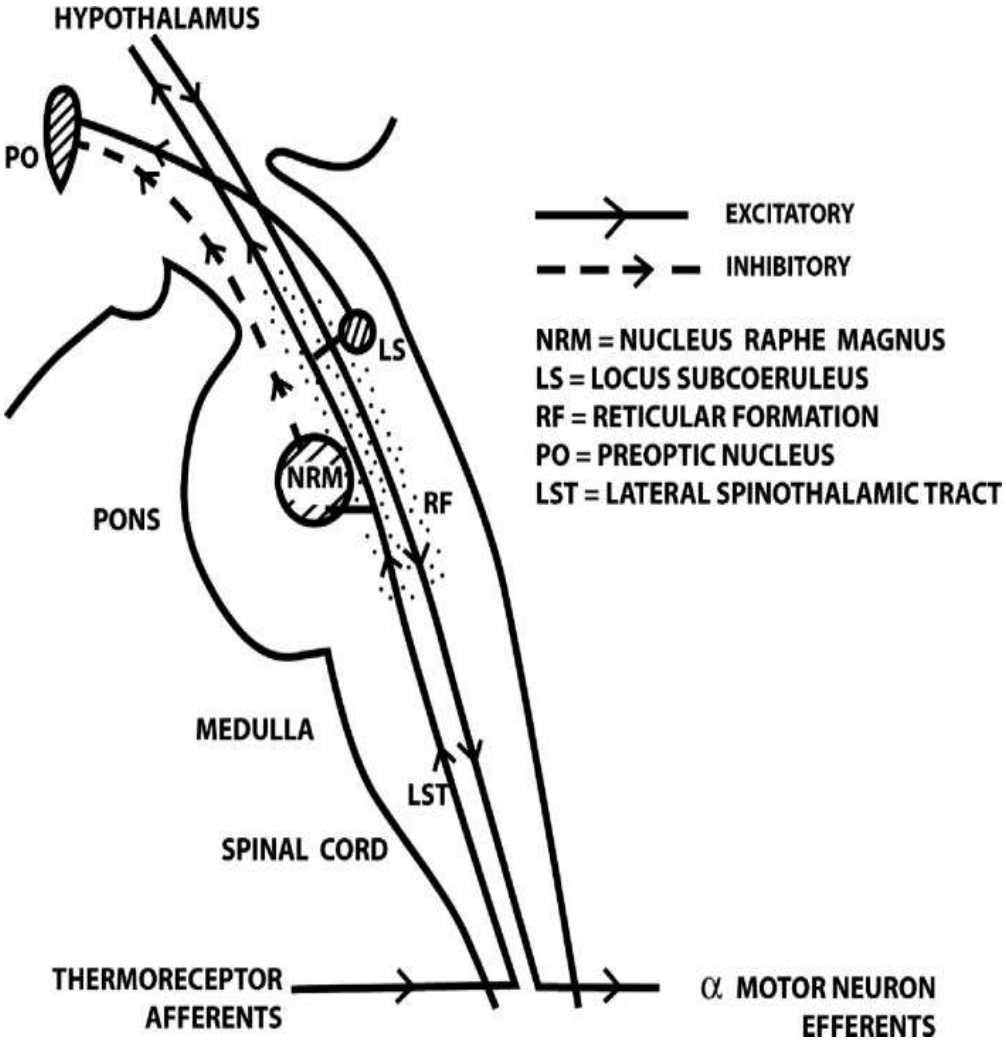
Fig 5: Skin temperature range for activating thermal receptors



CENTRAL REGULATION:

The autonomic thermoregulatory response, being the dominant response is controlled by the preoptic region of the hypothalamus. The anterior hypothalamus integrates afferent thermal information, whereas the posterior hypothalamus is majorly involved in controlling the descending pathways to effector site.

Fig 6: Schematic diagram of the shivering pathway



The temperature insensitive and temperature sensitive neurons are present in the preoptic neurons. The temperature insensitive neurons are responsive to non thermal stimuli like

the plasma osmolality, hormones, glucose levels, BP (Blood Pressure), CO_2, noxious and emotional stimuli. The temperature sensitive neurons are divided into heat and cold responsive neurons. The heat responsive neurons are 4 times more in number than the cold sensitive neurons. They increase their discharge rate and activate heat loss mechanisms in response to increased local heat. Cold responsive neurons get triggered when cold sensation from skin reaches the hypothalamic preoptic area. The hippocampus connects the limbic system and the thermoregulatory responses by the delivery of excitatory inputs to the warm responsive neurons. These neurons compare the thermal and non thermal inputs from spinal cord and also sense the core temperature. Though the hypothalamus integrates thermal information, majority are pre-processed in spinal cord and in other different parts of CNS before reaching hypothalamus.

The body temperature varies with circadian rhythm and during activities such as sleep mainly due to the changes in the neuronal activity in the ascending reticular activating system and suprachiasmatic nucleus which modulates the thermoregulatory centre in the hypothalamus[14,27].

The slope of response between intensity and core temperature is the gain of thermoregulatory response. When the response intensity doesnot increase even with further deviation in the core temperature, it is known as the maximum intensity. Various thermoregulatory responses like the vascular volume control and time dependent effects complicate the thermoregulatory system model of gains and threshold.

There are four neural mechanisms which are responsible for autonomic thermoregulation:

1. Peripheral cold detection

2. Central warmth detection

3. Inhibition of sweating by skin cooling.

4. Central inhibition of metabolic response to cold

The mechanism by which the absolute threshold temperature is determined is unknown but it is mediated by chemical mediators such as norepinephrine, acetylcholine, 5-11 HT3, dopamine, neuropeptides and prostaglandin E1. Threshold varies by approximately 0.5°C daily in both sexes and monthly in females during menstruation. It is affected by exercise, food intake, infection, hyperthyroidism, hypothyroidism, anaesthetic and other drugs, cold and warm adaptations.

Approximately 80% of control of autonomic response is determined by thermal input from core structures.[30] Whereas, a large fraction of behavioural response is derived from skin surface. The inter threshold range (core temperature not triggering autonomic thermoregulatory responses) is only 0.4°C (36.7°C to 37.1°C). This threshold has vasoconstriction at its lower end and sweating at its upper end. During general anaesthesia in volunteers this inter-threshold may be increased up to 4.0°C. The vasoconstriction and sweating thresholds are 0.3°C-0.5°C higher in women than men. In women, it is even more high in the follicular phase of menstrual cycle and also shows greater differences in luteal phase.[30] In premature neonates, central thermoregulatory control is somewhat intact when compared to elderly.[31]

EFFERENT THERMORECEPTORS

The effector system integrates multiple inputs into a single efferent signal. The effector mechanism in response to the thermal stimuli is either by the alteration of environmental heat loss or metabolic heat production. Each thermoregulatory effector has its own threshold and gain. Thus, there is an orderly progression of the responses and the response intensities in proportion to the need.[26]

The thermoregulatory responses are characterized by:

1. Behavioural alterations, the most effective method

2. Vasomotor response, leading to vasodilatation or vasoconstriction.

3. Shivering and increase in metabolic rate.[26]

The thermoregulatory effector triggers response at a particular temperature for a particular individual. Behavioural modification has a prominent role in conscious individuals to regulate the body temperature in comparison to the autonomic regulatory mechanisms. When an intense or noxious cold stimulus is perceived by the hypothalamus and when the impulses is transmitted to the cerebral cortex, behavioural modifications such as increased motor activity, adding clothing to self or moving to warmer surroundings.[26]

When the temperature range set between 36.7°C to 37.1°C is breached, the autonomic effector responses are activated. Either of the specific responses have a characteristic threshold, gain and maximum response intensity.

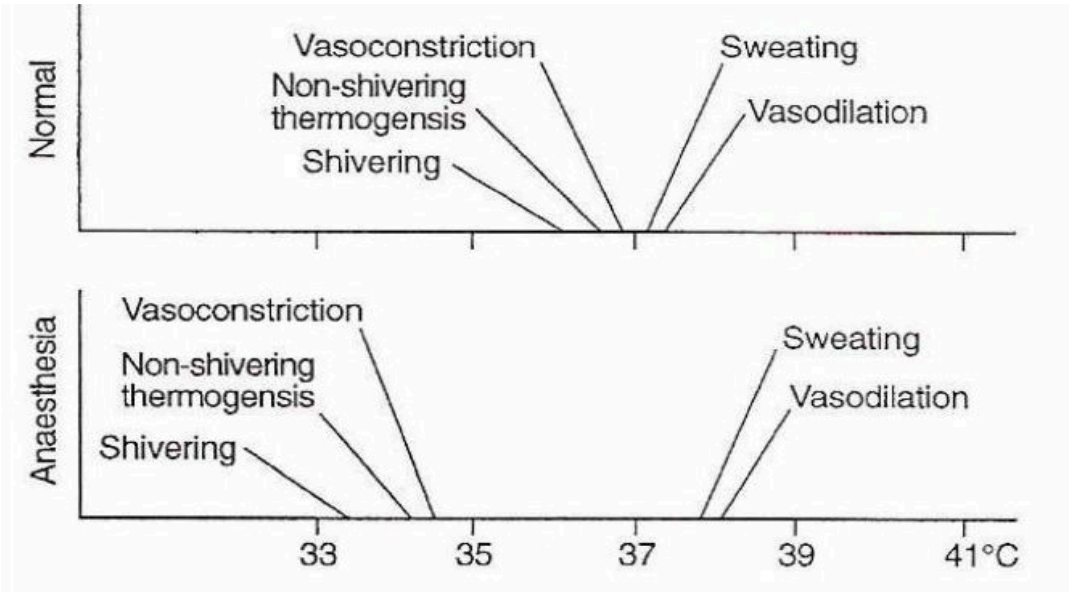


Fig 7: Thermoregulatory effector responses at specific temperatures in normal and anaesthetised individuals

Autonomic effector mechanisms, majorly vasomotor changes such as the cutaneous vasoconstriction and vasodilation without sweating or shivering is the most used autonomic effector mechanism.

The metabolic heat is preserved by thermoregulatory cutaneous vasoconstriction preventing a decrease in body temperature. Shivering is the last defence to be activated to maintain core body temperature following the failure of regulation by behavioural compensation and A-V shunt vasoconstriction. Metabolic heat is primarily lost through convection 15 and radiation from the surface of skin, vasoconstriction reduces this loss. The digital blood flow in total is divided into thermoregulatory (mostly A-V shunt) vasoconstriction and nutritional (mostly capillary).[26] The central temperature system has biologic rhythms. Fluctuations in core temperature occur daily with the lowest temperatures occurring in the early hours of morning in relation to melatonin secretion. These circadian rhythms can produce variation of up to 1.5°C.

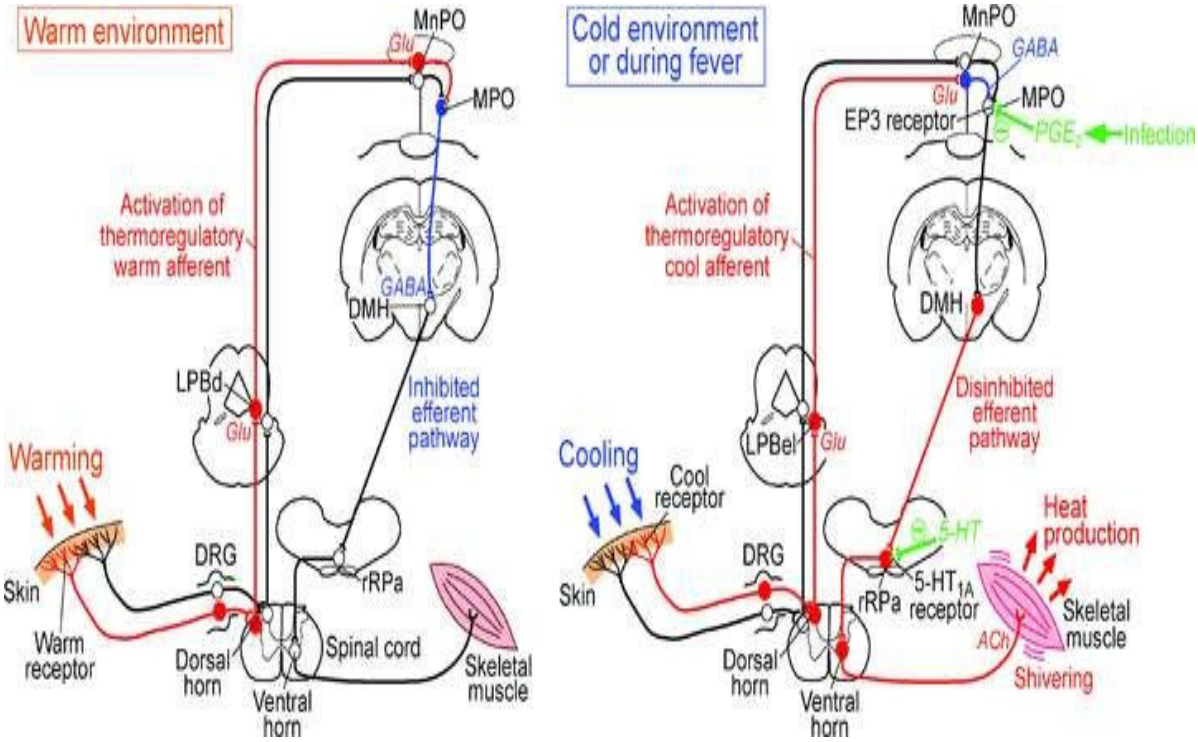


Fig 8: Thermoregulatory response to change in environmental temperature

Body response to hyperthermia

With rise in core body temperature above the threshold temperature, there is immediate dissipation of body heat to the environment by flushing and cutaneous vasodilatation which increases the heat transfer by 8 times to skin. It is followed by behavioral responses such as stretching out and increasing body surface area, sweating and pilo-relaxation.[32]

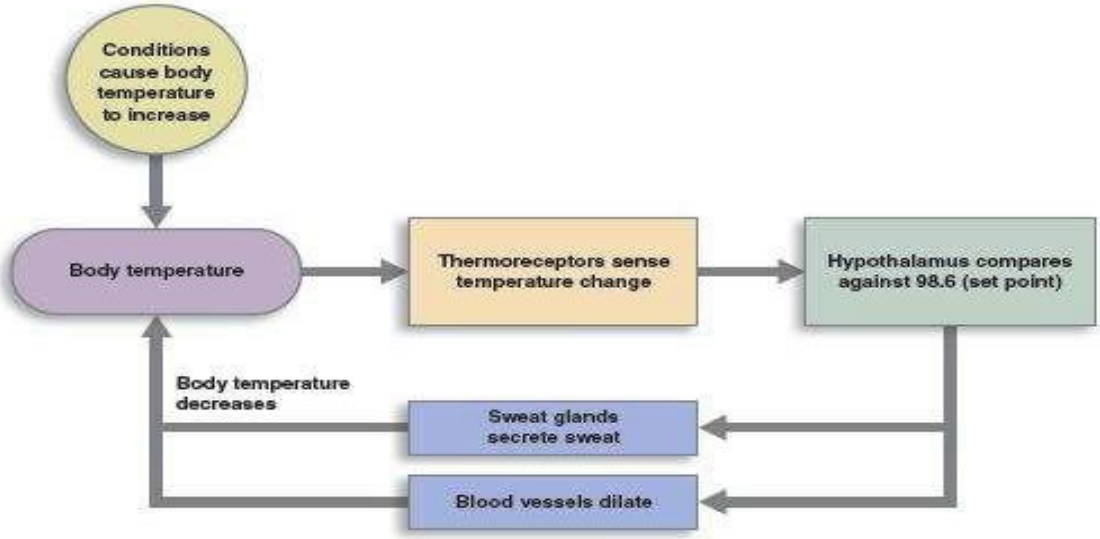


Fig 9: Body response to hyperthermia

Body response to hypothermia

The primary response to hypothermia in humans are cutaneous vasoconstriction, shivering and non-shivering thermogenesis. Cutaneous vasoconstriction is the most significant thermoregulatory response as it decreases cutaneous heat loss.[33]

Mitochondria, also known as the powerhouse of cells is responsible for generation of heat. Thermogenesis is attained by adrenergic stimulation which leads to increase in the basal metabolic rate (BMR) via uncoupling of oxidative phophorylation. Heat is generated in the muscle groups voluntarily by exercise and involuntarily by shivering.

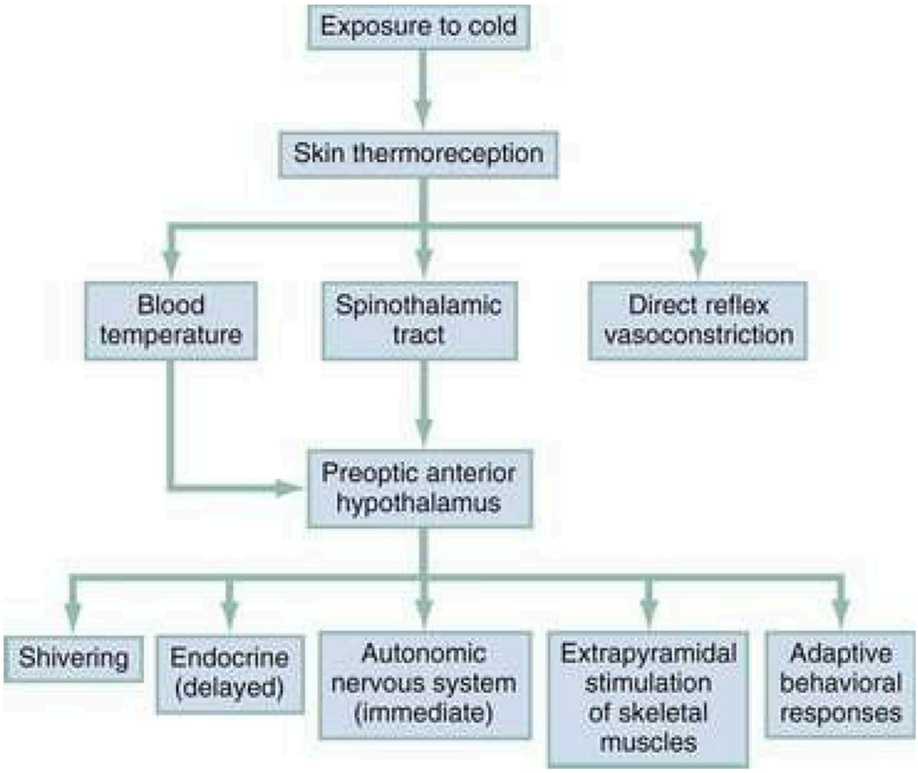


Fig 10: Body Response to hypothermia

SHIVERING

Shivering is an involuntary, oscillatory muscular activity. It is effective in increasing the heat production upto 600% in cases of vigorous shivering and increases oxygen consumption by 300 times. An electromyographic study in humans revealed that fundamental tremor frequency is around 200 Hz with waxing and waning of 4-8 cycles/min.[27]

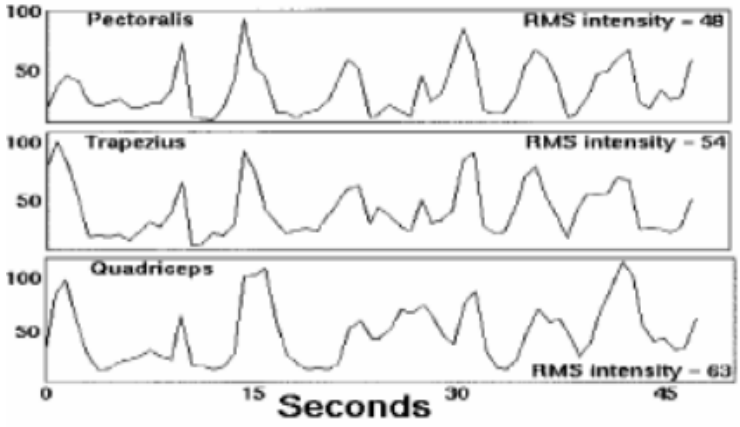


Fig 11: Patterns of shivering (waxing and waning)

The final pathway of a coordinated movement and shivering is by the spinal motor neurons and axons. A cold tremor appears as grouped discharges with a specific rhythm in the electromyography. The excitability of motor neurons and the cell size are inversely related. In the presence of a constant cold stimulus to the skin or spinal cord, motor neurons are recruited in the following order of increasing size[27]:

- small gamma motor neurons
- small tonic alpha motor neurons,
- larger phasic alpha motor neurons.

The larger neurons exhibit synchronized discharges when compared with smaller neurons. Synchronization of motor neurons during shivering may be facilitated by renshaw cell, interneurons which help in recurrent inhibition.[27]

Non shivering thermogenesis occurs in brown fat. It is the primary method of thermogenesis in neonates. Behavioral responses such as piloerection and curling up of body is seen in order to reduce the exposed surface in conditions of hypothermia. On prolonged exposure to cold, body compensates by acclimatization and also increases

BMR with the release of thyroxin.

In General anaesthesia, all 3 components are affected. Whereas in regional anaesthesia, the afferent and efferent components are affected which is responsible for the occurrence of perioperative hypothermia.

THERMOREGULATION DURING GENERAL ANAESTHESIA

Thermoregulation instability is observed during and after general anaesthesia. Most of the general anaesthetics inhibit autonomic thermoregulatory control, hence induction of anaesthesia impairs the role of neurons in the preoptic nuclei and hypothalamus, thereby decreasing the temperature at which compensatory responses are activated. In a patient who is under general anaesthesia, behavioural responses cannot be manifested. Anaesthetic drugs decrease the threshold to cold induced thermoregulation slightly elevates the warm response and markedly reduces cold response threshold. The inter-threshold range increases from 0.2°C which is the normal value to about 2°C-4°C. The gain and maximum intensity of some responses remain normal, whereas others are reduced by general anaesthesia.[26]

THERMOREGULATION DURING REGIONAL ANAESTHESIA

Central neuraxial blockade as seen in spinal and epidural anaesthesia, modifies the thermoregulatory response by reducing the vasoconstriction and threshold of shivering to 0.6°C which is comparable to general anaesthesia, but comparatively less when measured at the level above the upper level of the block.

In neuraxial block, impairment of thermoregulation is observed least when compared with combined general and neuraxial anaesthesia where it is seen maximum.[26] During anaesthesia, the decrease in core body temperature also depends on the duration of surgery. It can be divided into 3 phases:

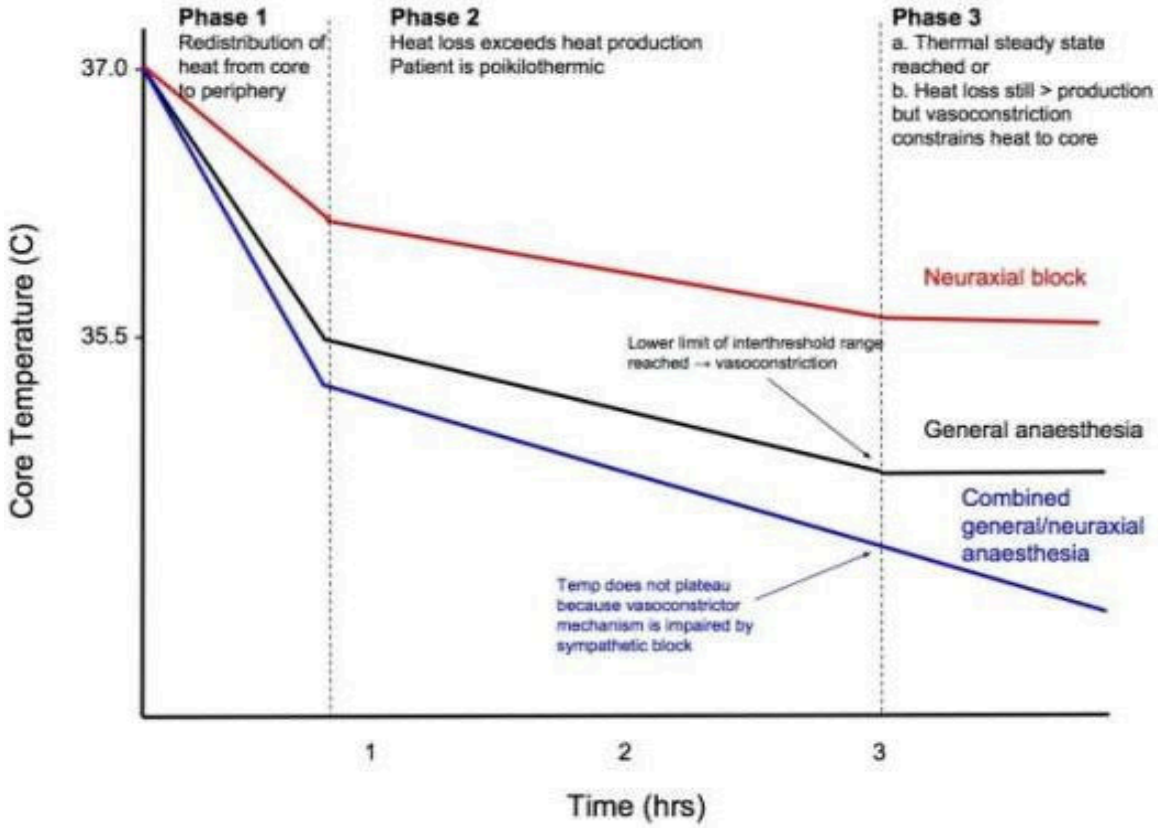


Fig 12: Phases of Intraoperative Hypothermia

Phase 1 (1hr, ↓ 0.5-1.5°C)

Anaesthesia induced vasodilatation causes rapid redistribution of heat from core to the periphery causing rapid decrease in core body temperature. The gradient of the core to peripheral temperature at the time of induction plays a role to determine the extent to which the redistribution reduces the core body temperature. A reduction of 20 - 30% of BMR decreases the heat production.

Phase 2 (2 - 4hrs, ↓ 1-3°C)

Heat loss exceeds the metabolic heat production leading to a slower and linear reduction in core body temperature.

Phase 3(>4 hrs, ↓ 2-4°C)

With time, a plateau is reached in the core temperature, representing the lower but stable thermal state by activating thermoregulatory vasoconstriction (heat production = heat loss). However, in extreme of ages, peripheral temperature continues to decrease such that heat loss is more than the heat produced.

POST ANAESTHETIC SHIVERING

Several theories have been put forward to explain post anaesthetic shivering. One such theory describes shivering as a spinal reflex hyperactivity, which is due to the inhibition of the descending cortical tracts controlled by the residual concentration of an anaesthetics. The electromyographic (EMG) signals give evidence to the clinical descriptions of abnormal reflexes observed during the early recovery phase.[5] A study was conducted to establish the relation between post-operative pain and shivering, stated that the presence of pain in patients who were not given local anaesthesia was accompanied by a higher incidence of post-anaesthetic shivering.[5] The most commonly accepted hypothesis states that shivering occurs as a result of thermoregulatory changes to hypothermia induced by anaesthesia. This hypothesis has been supported by comparing the EMG analysis of similar shivering patterns of people under anaesthesia and in a normal person.[5] Various studies have concluded that perioperative hypothermia, anaesthetic agents and post operative pain have a direct association with shivering. With the decrease in core body temperature, there is an internal redistribution of the heat content. Hypothermia and pain initiate the sympathetic overactivity which makes it difficult to assess the effect of sympathetic overactivity on postanaesthetic shivering.[5]

CONSEQUENCES OF POST ANAESTHETIC SHIVERING

Shivering is a stressful condition for the patient as well as the physician as it interferes with patient monitoring and also having the following consequences:

1. Patient discomfort
2. Gives abnormal or miscalculated values
3. Increase in BMR
4. Increased blood loss
5. Increased oxygen consumption
6. Delayed wound healing
7. Increased risk of infection
8. Impaired or delayed drug metabolism
9. Increased intracranial and intraocular pressures

10. Platelet dysfunction

11. Increased post- operative pain

12. left shift of haemoglobin – oxygen dissociation curve

13. cardiac arrhythmias and Ischemia

PREVENTION OF SHIVERING:

Heat is lost to the environment by radiation, conduction and convection. Measures which can decrease the core hypothermia in turn reduces anaesthesia induced shivering. This can be achieved by:

1. Mechanical - passive insulation and active warming

2. Chemical - pre-emptive pharmacotherapy

1. Passive insulation - It includes covering the body with cotton blankets, cloth or paper surgical drapes, disposable plastic drapes and plastic bags. Passive insulators decrease the heat loss to the environment upto 20-30% when a single layer of covering is used. However, addition of extra layers do not proportionally increase the benefit. This method is not beneficial in longer duration and extensive surgeries.

2. Active warming - Convection warming system uses warmed air forced through a quilt like porous blanket over the skin, it directly warms and also replaces the normal body "air envelope" with a warm air envelop. This turns out to be the most effective system for body heat conservation. Radiant heat system such as the infrared light and the thermal ceiling lights can be used for body warming. Other measures such as warming the inspired air, intravenous fluids, blood products before infusion and maintaining warmer post-operative environment are useful in conserving the body temperature and hence reduces shivering.

3. Pharmacotherapy

Various cholinomimetics, biogenic monoamines, endogenous peptides, cations and NMDA receptor antagonists such as analgesics and sedatives have been used as potent antishivering agents. A thermo-modulation occurs at peripheral receptors, the level of spinal cord or central level by acting at one or more of the above mentioned receptor sites.

i. **Nefopam:-** Primarily analgesic with a potent antishivering property acts via an increase in the activity of serotonin, nor epinephrine and dopamine.

ii. **Clonidine and Dexmedetomidine**:- they inhibit shivering due to their central alpha 2adrenergic receptor agonist property.

iii. **Magnesium Sulfate**:- NMDA receptor antagonist with antishivering property.

iv. **Ketamine**:- Competitive NMDA receptor antagonist used for shivering control.

v. **Opioids:-** Morphine, fentanyl, sufentanyl, pentazocine, nalbuphine, buprenorphine in low doses are helpful to control shivering due to their action on kappa-Opioid receptors.

vi. **Tramadol:-** along with the action on kappa opioid receptors, it help in the control of shivering by preventing the reuptake of hydroxytryptamine and norepinephrine.

vii. **Serotonin receptors antagonists**:- its anti-shivering effect is via inhibition of the reuptake of serotonin in the pre-optic region of anterior hypothalamus.

PERIOPERATIVE TEMPERATURE MONITORING

Body temperature is heterogenous: the core body temperature in places such as thorax, abdomen and central nervous system usually vary 2 to 4°C higher when compared with the peripheral tissues. The skin surface which is still cooler depends on environmental factors such as ambient temperature, air speed and peripheral perfusion. The temperature of peripheral tissues (arms and legs) depends on present exposure, core temperature and vasomotion. Core body temperature is characterized by body heat content and distribution. It is the single best indicator of thermal status in humans as it controls majority of autonomic thermoregulatory control.[12,34]

Temperature monitoring is an integral part of perioperative monitoring. In 1868, thermometry was first used clinically after publication of a study by Carl Wunderlich which concluded that normal body temperature varies ±0.5°C from about 37°C. Various devices have been used for temperature monitoring, namely[35]:

1. Thermistors
2. Thermocouplers
3. Infrared thermometer
4. Zero heat flux thermometry

Thermistors and thermocouples are the most commonly used thermometers. Thermistors are temperature-sensitive semi-conductors, whereas thermocouples depend on the tiny thermoelectric voltages generated when dissimilar metals are joined. Both these devices are accurate for clinical use and inexpensive. Infrared thermometers have an advantage of estimating temperature from a distance. Tympanic membrane thermometers are a popular example of infrared thermometers.[12,35]

Core body temperature monitoring is required for most patients undergoing general or neuraxial anaesthesia for more than 30 minutes, to detect the occurrence of hyperthermia, hypothermia and malignant hyperthermia. However, temperature monitoring is seldom practised. Thus, a significant amount of thermoregulation instability often goes undetected in many patients.[34]

SITES OF MONITORING

i. CORE TEMPERATURE
ii. NEAR CORE TEMPERATURE

CORE TEMPERATURE:

The core thermal compartment can be measured from sites which are highly vascularized from the core. Even in the presence of thermal unrests such as cardio-pulmonary bypass, these monitoring sites remain reliable despite transient differences in real time.[34] Core body temperatures can be measured from sites such as

i. **Pulmonary artery** - rarely available but best estimate of core temperature[34]
ii. **Distal oesophagus** - most used during general anaesthesia. It is monitored with the help of a thermocouple or thermistor incorporated into an oesophageal stethoscope.[34]
iii. **Nasopharynx** - alternative to oesophageal monitoring. It is inserted 10cm to 20cms from the nares.[34]
iv. **Tympanic membrane** thermometers:

These are based on the principle that all objects emit electromagnetic radiation over a wide range of wavelength for which the intensity of emitted radiation is maximum depend on the temperature of the object. Objects at body temperature primarily emit infrared radiation. The infrared thermometer uses a tube inserted into the ear canal to direct the signal into an electric signal. Tympanic membrane thermometers are to be inserted further into the ear so that they receive radiation only from the tympanic membrane, which is more representative of the core temperature than the ear canal.[34]

Disadvantages:

i. Intermittent measurement
ii. Poor penetration and obstruction due to impacted wax
iii. Assosciated perforation of the ear canal can be a problem.

NEAR CORE TEMPERATURES:

i. Axillary temperature:

It is relatively close to core body temperature and may be reasonable in selected patients. It measures temperature at the surface of skin and on the opposite side of the device, allowing it to compensate for changes in arm position and ambient temperature.[34]

ii. Bladder Temperature & rectal Temperatures:

They are less reliable as these sites are poorly vascularized and thus lag core temperature during rapid thermal disturbances. Its accuracy decreases in states of decreased urine output.[34]

Monitoring of the vital signs and temperature during the surgery is necessary for preventing hypothermia and its assosciated complications such as patient discomfort, cardiac morbidity, wound infection and surgical bleeding. [34,35]

PHARMACOLOGY OF RAMOSETRON

Ramosetron hydrochloride is a newer anti-emetic drug in the group of selective 5-HT3 receptor antagonist. In Japan 1996, it was initially launched and marketed as a treatment for nausea and vomiting induced post chemotherapy or other gastro-intestinal symptoms. Though 5-HT3 receptors have a wide range of functions such as emesis, cognition and anxiety, it has been approved only for the prevention of nausea & vomiting. Ramosetron is now widely used as a first line treatment of post-operative nausea and vomiting in view of its safety and efficacy.

Ramosetron is a highly potent drug derived from tetra hydrobenzimidazole with an indole ring. 5-HT3 receptor is a ligand-gated channel belonging to the GABA/Nicotine receptor family, whereas the other 5-HT receptors belong to the family of G-protein-coupled receptors.

Chemical formula: C17H17N3O

Molecular mass: 279.33

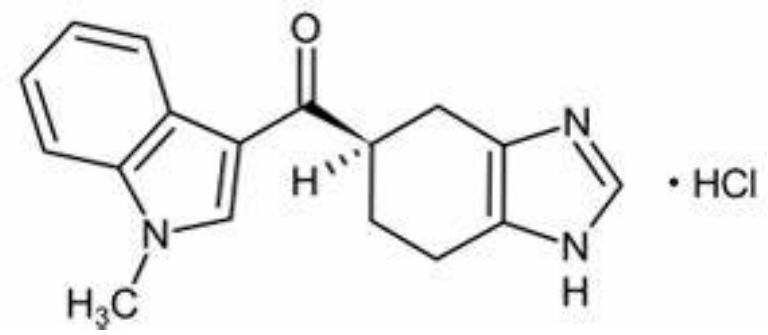


Fig 13: Chemical formula of ramosetron

PHARMACODYNAMICS:

Ramosetron selectively blocks 5-HT3 receptor. Serotonin plays an important role in neurotransmission and hence the visceral reflexes, pain, itch, emesis, bradycardia, hypotension due to sympathetic tone withdrawal and shivering. The anti-shivering effect of ramosetron is by inhibiting reuptake of serotonin at the pre-optic region of anterior hypothalamus.

PHARMACOKINETICS

It is best described with a 3 compartment mammillary model with first-order elimination.[36]

In comparison with the first generation 5-HT3 antagonists, ramosetron has higher potency and a longer antiemetic action. It has a widespread hepatic oxidative metabolism which is mediated via multiple cytochrome P450 forms, majorly by CYP1A2 and CYP2D6.

After oral or intravenous administration, Ramosetron hydrochloride achieves Cmax after 2 hours with a plasma half-life of 5 hours to 6 hours. The Cmax and AUC are linear activity in nature and dose-dependent. The oral bioavailability of Ramosetron hydrochloride is about 50%. The drug is widely distributed in the body fluids including breast milk. Ramosetron hydrochloride is excreted via urine as drug metabolites and as unaltered drug.

DOSAGE

Intravenous dose : 0.3mg
Maximum dose/day : 10mcg

DRUG INTERACTIONS

Few drugs which cause severe gastro-intestinal disturbances when co-administered with ramosetron are:

- CYP1A2 inhibitors
- MAOIs
- Anti-psychotics,
- Phenothiazines
- Anticholinergics
- Opioid narcotic
- Tricyclic anti-depressants

CONTRAINDICATIONS:

- Constipation predominant IBS
- Active diarrhoea
- Colon cancer.
- Hypersensitivity
- Pregnancy - USFDA Category C, may or may not be harmful to foetus.
- Lactation - in breast milk.

MATERIALS AND METHODS

Patients who are aged between 18 & 60 yrs of both genders, who belong to the ASA grade I & II, undergoing elective surgical procedure in supine position with spinal anaesthesia at "KLE's Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi -10" during the period of January 2020 to March 2021.

Study design: A One Year Hospital Based Double Blinded Randomized Clinical Trial.

Sample size: Total sample size: 70

Sampling procedure: Randomization was achieved by computer generated randomization chart.

Sample size calculation: "The minimum sample size formula based on two proportions is

$$n = \frac{(z_\alpha + z_\beta)^2 \bar{p}(1-\bar{p})}{d^2}$$

where p_1 and p_2 are the proportions of the two groups.

$p = \frac{p_1 + p_2}{2}$ and $d = p_1 - p_2$

zα is linked with the level of significance and zβ is linked with the power of the test. For 5% level of the significance zα = 1.96 and zβ = 0.84 for 80% power of the test."

REFERENCE: "Rohit K.V, Megha G, Kali K., Gurdeep S.J. The role of ramosetron in the prevention of post-spinal shivering in obstetric patients. A prospective randomized double blind study."

By taking proportion of success, p_1 = 53.8% and p_2 = 21.0% the sample size obtained is 68.

There would be two groups of 35 each.

Place:

"KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Jawaharlal Nehru Medical College, Belagavi."

Selection Criteria:

Inclusion Criteria:

- Patients undergoing elective infraumbilical surgeries.
- ASA physical grade I & II.
- Age between 18 - 60 yrs.
- Patients undergoing elective surgeries under spinal anaesthesia.
- Provides Consent.

Exclusion Criteria:

- Patient who are unable to give consent.
- ASA physical status III or more.
- Patient undergoing emergency surgery.
- Patient allergic to the drug under study.
- Patients with contraindication to spinal anaesthesia.
- Patients who are on chronic opioid medication.

METHODOLOGY

After obtaining the clearance from the ethical board & written informed consent, 70 patients who are to undergo surgery under spinal anaesthesia have been included in the study.

After having met both the inclusion & exclusion criteria, computer generated randomization was used to randomize patients into either of the 2 groups.

Group A: Patients in whom ramosetron 0.3mg was given.

Group B: Patients in whom placebo (normal saline) was given.

A through pre-anaesthetic evaluation was done on the day before surgery. FBS, Complete blood picture was done in all patients. X-Ray and ECG was done in patients over 40 yrs of age.

On the day of surgery, intravenous access was secured using 18G or 20 G iv cannula and i.v fluids were started.

Standard monitoring devices were attached before induction of anaesthesia, including non-invasive blood pressure, heart rate, ECG and oxygen saturation.

Patients were put in left lateral position and under strict aseptic conditions 3.5ml of 0.5% (H) Bupivacaine was given with a 23G spinal needle in L2-L3 sub arachnoid space. Patient was made supine. Baseline pulse, BP, SpO2 was noted after spinal anaesthesia. Ramosetron 0.3mg (2ml of drug diluted till 4ml) and placebo i.e, normal saline (4ml) was given slowly i.v over 1minute as per the randomization done by computer.

The syringes were identical and made by an anaesthetist not involved in the study. This helped in blinding the anaesthetist in the study to record his/her observation.

With the help of a tympanic thermometer, the core body temperature was measured for every 30 minutes for upto 3hours. Shivering was checked for every 10 minutes for the first 30 minutes followed by every 15 minutes for a period of 3hours. The time of onset of shivering if any was noted till a period of 3hours.

Shivering was taken as the primary outcome and was observed and categorized by an observer who was blinded to the study group throughout the intra operative period. A grading scale given by **Crossley** and **Mahajan**, and **Tsai** and **Chu** was used:

"0 - No shivering.

1 - Piloerection or peripheral vasoconstriction but no visible shivering.

2 – Muscular activity in only one muscle group.

3 - Muscular activity in more than one muscle group but not generalized shivering.

4 – Shivering involving the whole body."

Shivering was considered positive if grade 2-4 shivering is present for more than 3 minutes. The observed findings were recorded accordingly in the tables mentioned below.

TIME OF (mins)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Spinal					
T0(Study Drug)					
T10					
T20					
T30					
T45					
T60					
T75					
T90					
T105					
T120					
T135					
T150					
T165					
T180					

Time of measurement (mins)	Core body temperature
At spinal	
At study drug	
T30	
T60	
T90	
T120	
T150	
T180	

The side effects of drug under study if any were noted. Any shivering complained by the patient was treated with tramadol 1mg/kg slow intravenously.

Intraoperatively – onset and duration of sensory block as well as onset and duration of motor block was noted.

SpO2, Pulse rate and BP was measured every 5minutes till the end of surgery. Any fall in BP more than 20% of baseline was treated with Inj. Ephedrine 6mg and repeated if necessary. Fall in heart rate more than 20% of baseline was considered bradycardia and was treated by Inj. Atropine 0.01mg/kg i.v.

Statistical Analysis;

The study is focused on comparison of two groups. For the continuous quantitative variables mean and standard deviation was calculated. The inter group continuous variables were compared using suitable tools of statistics like unpaired student's t test. Two quantitative variables within a group, were compared using student's paired t test.

Discrete variables were represented by median. Suitable graphs were used to depict the comparison.

The categorical data was expressed in terms of rates, ratios and percentages. The association between the outcome, clinical and demographic characteristics was tested using Chi-square test or Fisher's exact test.

Nonparametric tests were used for discrete variables. For all the tests the value of p less than 5% (0.05) was considered significant.

RESULTS

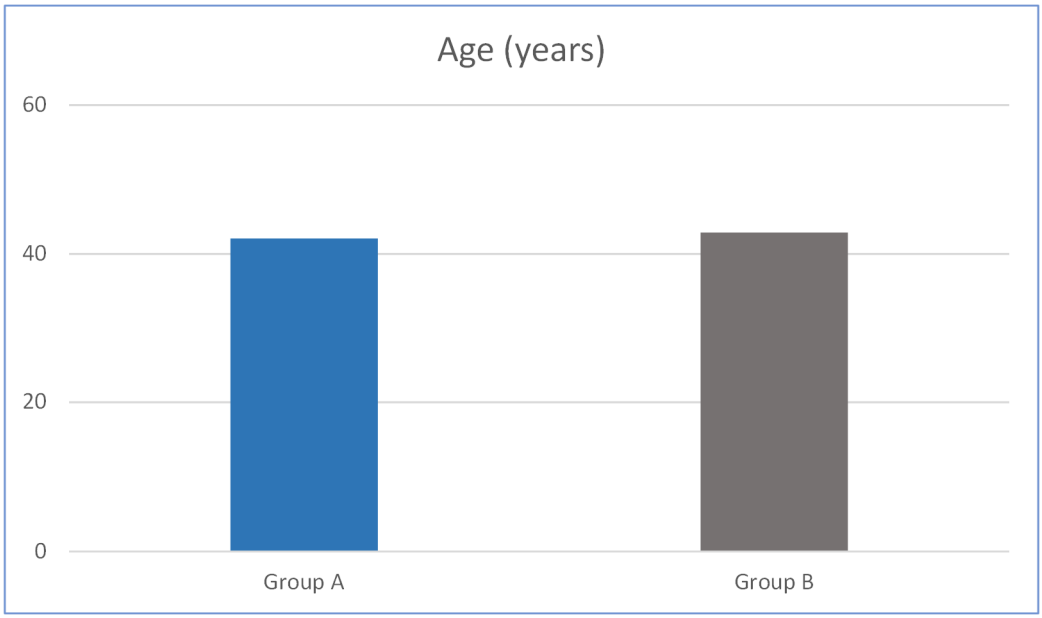
This study was conducted to evaluate the efficacy of ramosetron to prevent shivering in patients undergoing surgery under spinal anesthesia.

70 patients have been enrolled in the study. Considering both inclusion & exclusion criteria, 35 patients in Group A received ramosetron 0.3 mg and 35 patients in Group B received normal saline.

DEMOGRAPHIC DATA:

Table 1: Mean Age

	Group A		Group B		p value
	Mean	Standard Deviation(SD)	Mean	Standard Deviation(SD)	
Age (years)	42.09	10.34	42.9	13.20	0.9177

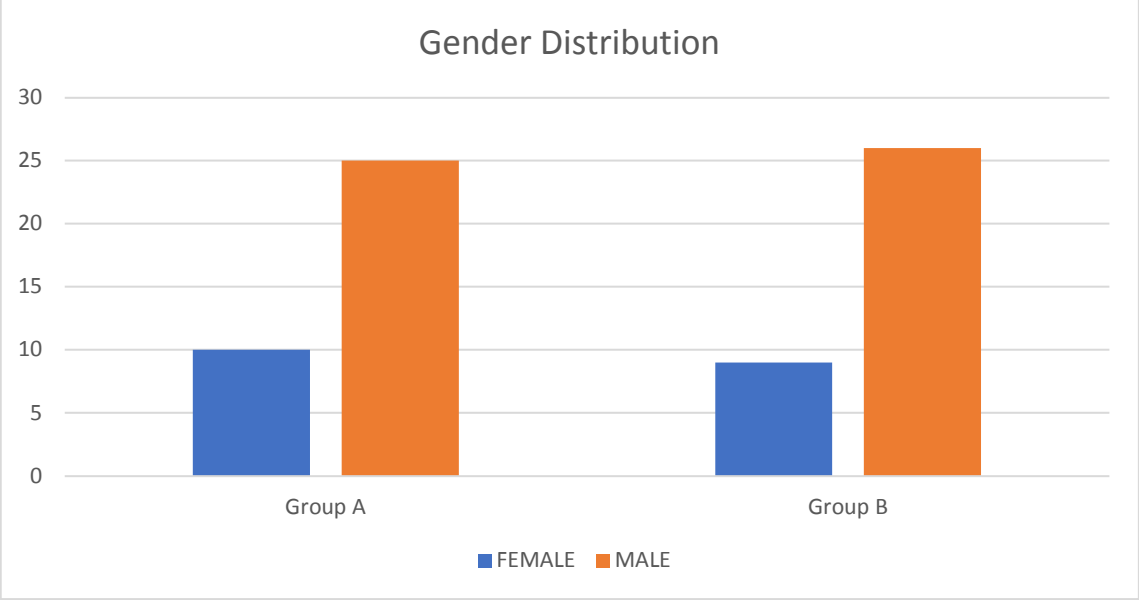


Graph 1: Mean Age.

In our study, there has been no statistical difference which was significant between Groups A & B with regards to mean age (42.09±10.34 years, 42.90±13.20 years respectively; p =0.9177). The p value was calculated using student's unpaired 't' test.

Table 2: Gender Distribution

GENDER	Group A	Group B	P value
FEMALE	10	9	
MALE	25	26	
TOTAL	35	35	0.7881

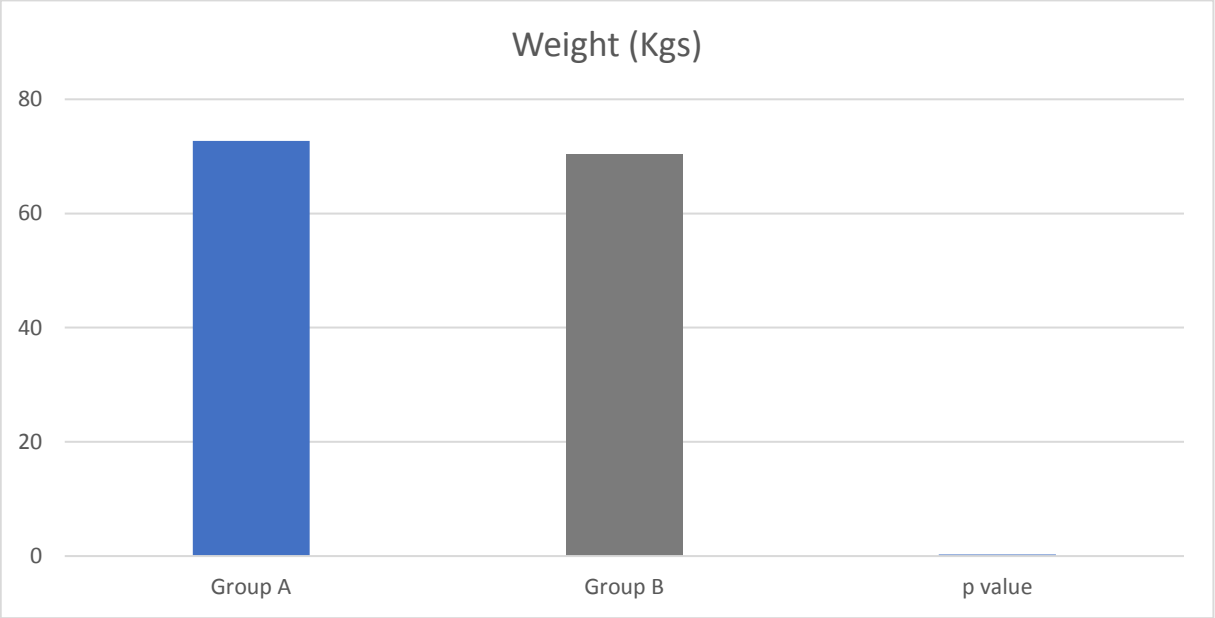


Graph 2: Gender Distribution

Out of 35 patients in Group A, 10 were female & 25 were male. Out of the total 35 patients in Group B, 9 were female & 26 were males with a p value of 0.7881. Both the groups had similar demographic characteristics.

Table 3: Mean Weight

	Group A		Group B		p value
	Mean	SD	Mean	SD	
Weight (Kgs)	72.71	8.14	70.43	9.50	0.2837

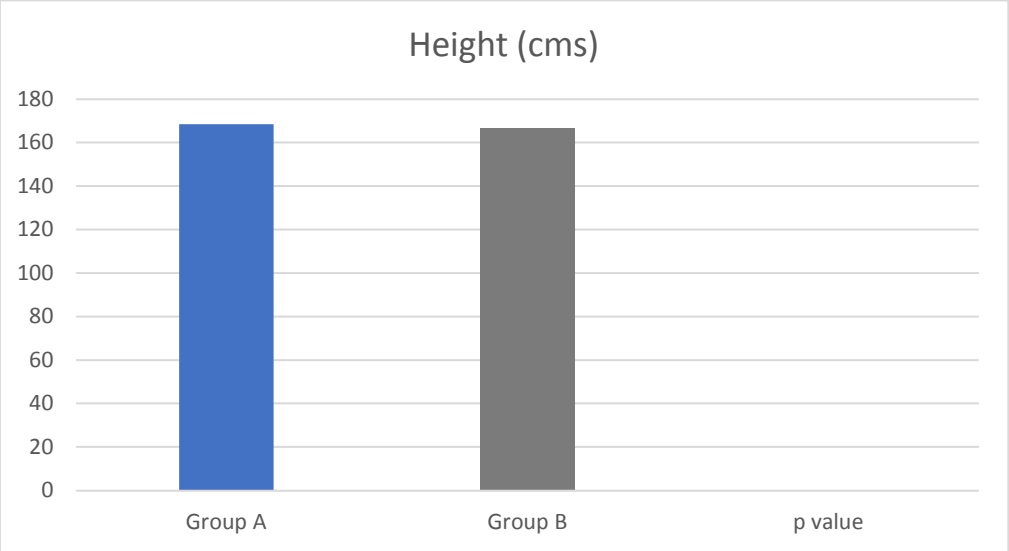


Graph 3: Mean Weight

In our study, no significant difference has been found between Groups A & B when mean weight was considered (72.71±8.14 kgs, 70.43±9.50 kgs respectively; p =0.2837). The p value was calculated using student's unpaired 't' test.

Table 4: Mean Height

	Group A		Group B		p value
	Mean	SD	Mean	SD	
Height (cms)	168.46	4.68	166.63	6.11	0.1645

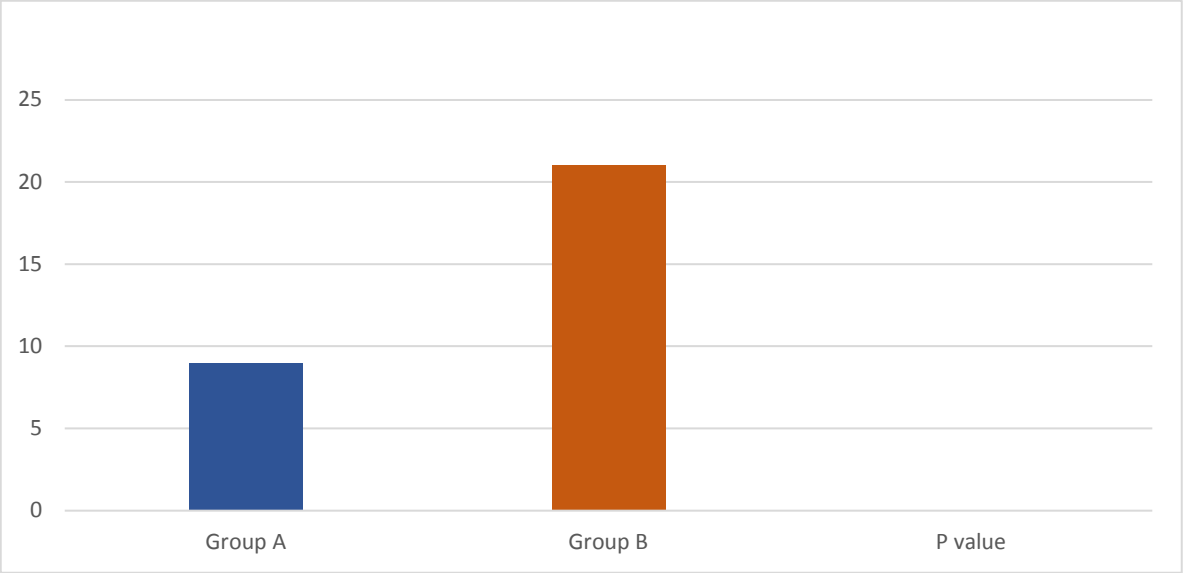


Graph 4: Mean Height

In our study, no significant difference has been found between Groups A & B with reference to average height (168.46±4.68 cms, 166.63±6.11 cms respectively; p =0.1645). The p value was calculated using student's unpaired 't' test.

Table 5: Incidence Of Shivering

Group A	Group B	P value	INFERENCE
9	21	<0.0001	HS

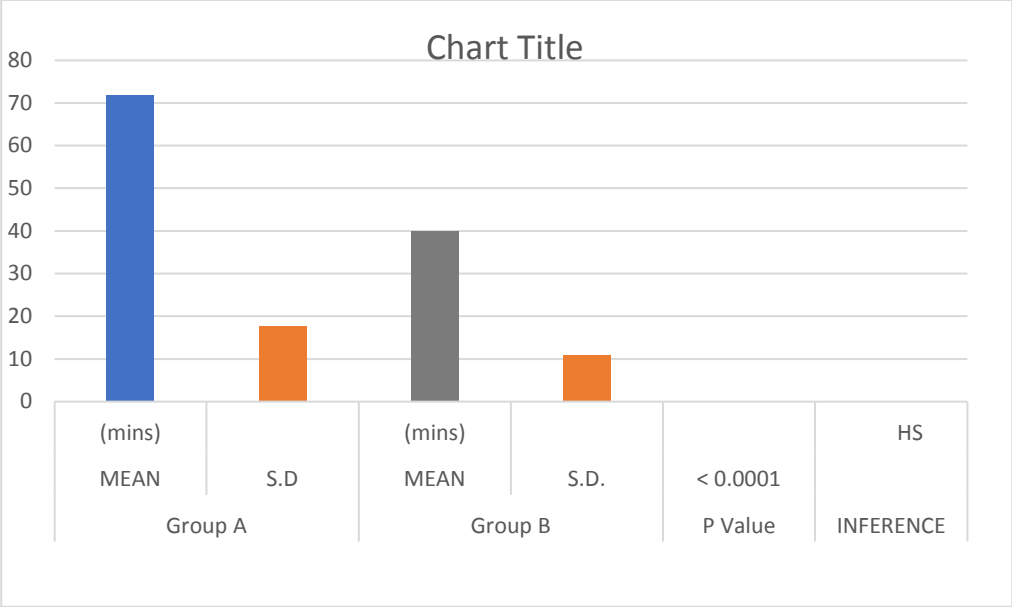


Graph 5: Incidence Of Shivering

In this study, a highly significant difference has been observed with regards to incidence of shivering. 9 out of 35 patients of Group A developed shivering. However, in Group B shivering has been recorded in 21 of 35 patients.

Table 6: Onset Of Shivering

Group A				Group B				P Value	INFERENCE
MEAN (mins)	S.D	MIN	MAX	MEAN (mins)	S.D.	MIN	MAX	< 0.0001	HS
71.88	17.72	45	105	40	11	30	60		

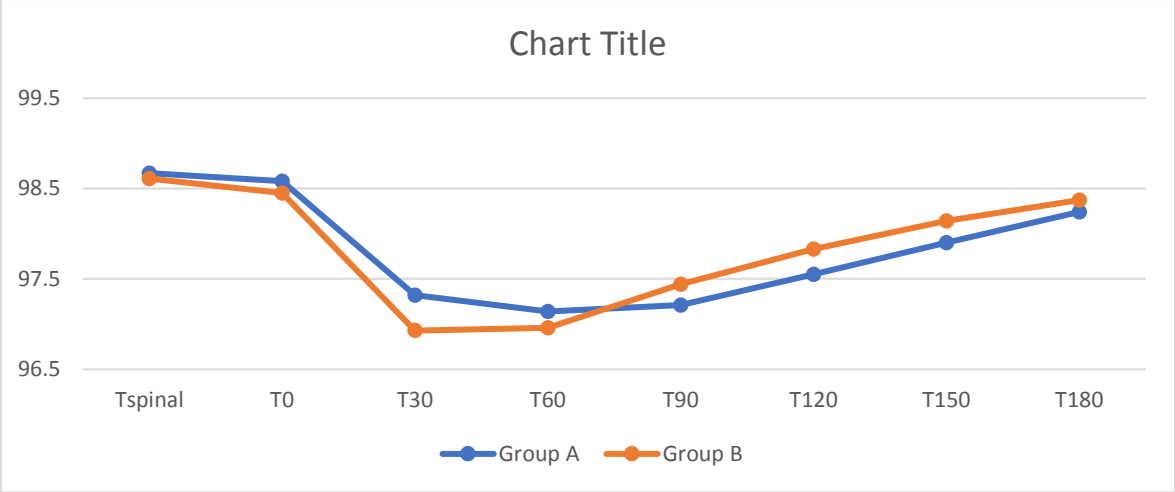


Graph 6: Onset Of Shivering

On comparing the onset of shivering amongst the two groups, the results obtained were highly significant. The mean duration of onset of shivering after spinal anaesthesia was 71.8 minutes in the Group A and 40 minutes in Group B.

Table 7: Mean Core Body Temperature (degree Fahrenheit)

	Group A				Group B					
	MEAN	**S.D.**	**MINIMUM**	**MAXIMUM**	**MEAN**	**S.D.**	**MINIMUM**	**MAXIMUM**	**p VALUE**	**INFERENCE**
Tspinal	98.67	0.15	98	98.8	98.61	0.13	98.4	98.9	0.0675	NS
T_0	98.58	0.25	97.3	98.9	98.45	0.13	98.2	98.7	0.0110	S
T_{30}	97.32	0.29	96.6	98	96.93	0.24	96.5	97.3	< 0.0001	HS
T_{60}	97.14	0.23	96.4	97.5	96.96	0.35	96.2	97.6	0.0156	S
T_{90}	97.21	0.31	96.6	97.9	97.44	0.22	97.1	97.9	0.0115	S
T_{120}	97.55	0.26	97	98	97.83	0.16	97.5	98	0.0002	HS
T_{150}	97.90	0.19	97.3	98.1	98.14	0.10	98	98.3	< 0.0001	HS
T_{180}	98.24	0.23	97.5	98.5	98.37	0.08	98.2	98.5	0.0289	S



Graph 7: Mean Core Body Temperature.

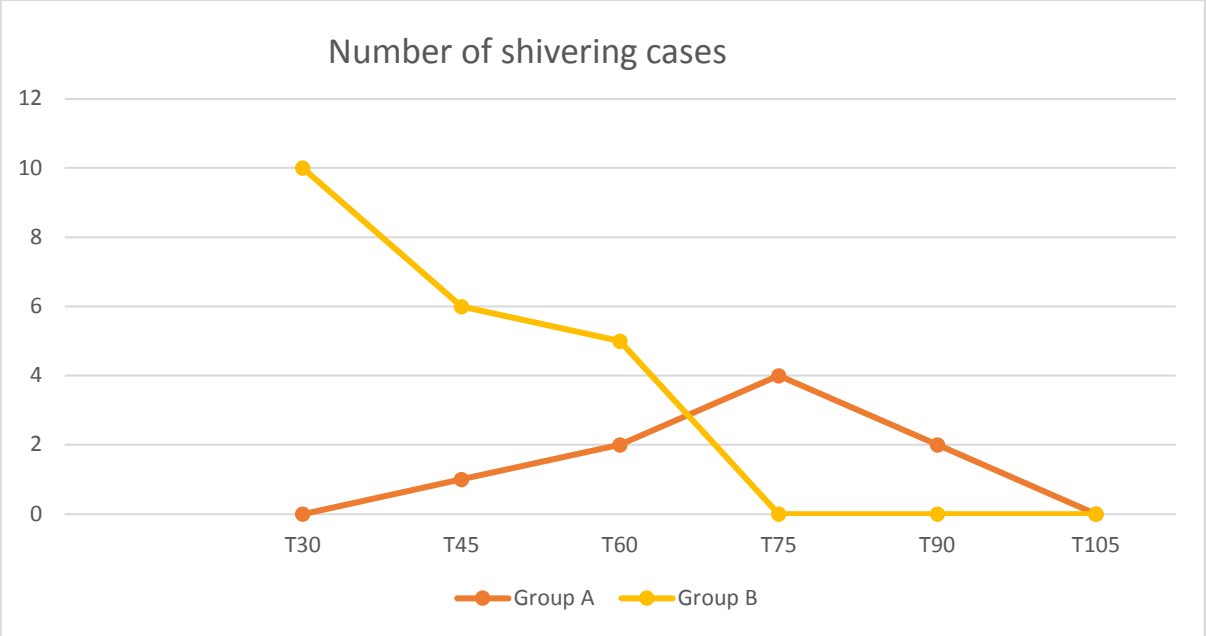
The mean temperature of the patients at the time of giving spinal anaesthesia in the Group A & Group B are 98.67^0F & 98.61^0F respectively. These recordings were comparable and were not significantly different. Whereas 30 minutes after the procedure of spinal anaesthesia, the drop in the mean temperature from the baseline was significant in both the groups. The mean temperatures recorded at T30 were 97.32^0F in Group A and 96.5^0F in Group B. The difference in the temperature between the two groups at T30 is highly significant.

This significant difference in mean temperatures at various time periods post spinal has been maintained between the two groups during the monitoring period of 3 hours.

Table 8: TIME POINTS WHEN SHIVERING WAS NOTICED

	TIME POINTS WHEN SHIVERING WAS NOTICED						
	T_{30}	T_{45}	T_{60}	T_{75}	T_{90}	T_{105}	TOTAL
Group A	0	1	2	4	2	0	9
Group B	10	6	5	0	0	0	21

At a given time period T30, shivering was observed in 10 patients in Group B whereas no one shivered in Group A. At T45, 1 patient in Group A shivered compared to the 6 patients who shivered in Group B. At T60, shivering was observed in 2 patients in Group A & 5 patients in Group B. In Group A, at T75 4 patients shivered. The p value using Chi-square test is 0.0011(VS).



Graph 8: Number of patients who were shivering at a given point of time

DISCUSSION

The normal human body temperature is maintained between a narrow range of $97^{O}F$ to $99^{O}F$, which is necessary for normal physiologic and metabolic functions. The core body temperature is controlled and stabilized mainly by anterior hypothalamic nuclei & preoptic area of hypothalamus, an area of the brain which links the endocrine system to the nervous system. When the core body temperature varies from the set point, there is initiation of the control mechanisms which increase or reduce the energy production or dissipation as required to return the temperature towards set point.

An unpleasant condition such as shivering is a frequently occuring problem confronted by the anaesthesiologist during the peri-operative period following SAB. The physiological role of shivering is mainly to provide heat, nevertheless its incidence in anaesthesia is inconsistent and not well understood. Under regional anaesthesia, the most probable mechanism being either a result of decrease in core body temperature, misinformation from receptors or impairments of physiologic set points.

Various factors which contribute to post-spinal shivering include- uninhibited spinal reflexes, sympathetic block leading to peripheral vasodilatation, improved cutaneous blood flow leading to an increase in heat loss via the skin, colder operating room, rapid i.v infusion of colder fluids, suppression of the adrenals, the release of pyrogenic mediators during surgical pain, loss of blood, duration of surgery & thermoregulatory shivering in response to intraoperative hypothermia. Intra-operative hypothermia is one of the major risk factors for PSS. However, even normothermic patients can still shiver at the end of procedure.[37]

The search for an ideal anti-shivering drug with least side effects is still ongoing. Numerous drugs such as tramadol, pethidine, ketamine, dexmedetomidine which have been used in the past for the treatment of PSS are associated with undesirable side effects.

For eg: pethidine & tramadol produce respiratory depression & nausea and vomiting respectively.

Several studies were available for the treatment of intra-operative shivering but only few studies were available for the prevention of shivering by preventive administration of anti-shivering agents. 5 HT3 antagonists are proven to be highly efficacious in preventing PONV & does not produce any noteworthy side effects.

In one study conducted by Badawy and Mokhtar, the role of ondansetron for prevention of post-spinal shivering in parturients has been experimented. A statistically significant difference has been observed in the incidence of Post spinal shivering in the ondansetron group 26% in comparison to the normal saline group 51% (P = 0.007) & the incidence for maximum shivering at any given period was 8/37 (22%) vs. 3/38 (7.8%) (P = 0.004). Shakya et al. conducted a study on patients who underwent lower abdominal surgeries under subarachnoid block. They concluded that 10% of the patients who were given ondansetron had post-spinal shivering as compared to 42.5% in the control group.[38] Ondansetron belongs to the same class of drugs with a similar mechanism of action and pharmacokinetics as ramosetron. However, on comparison ramosetron is more effective with fewer adverse effects.

Dolasetron, ondansetron and granisetron are 5-HT3-receptor antagonists, which were tested to be effective to ease postoperative shivering. Their mechanism is still not clear but is thought to exert its effect by inhibiting the reuptake of the serotonin on the preoptic region of anterior hypothalamus. In a study conducted by Powell and Buggy, they found that 57% of patients from the control group who did not receive any drug exhibited shivering after general anaesthesia when compared to patients who received 4mg or 8mg ondansetron exhibited 33% and 15% respectively. They concluded that the administration of ondansetron 8mg was even more effective than 4 mg of ondansetron for shivering in

the patients. The consequence of ondansetron was not dependent on the core hypothermia intraoperatively, which suggests that the thermoregulatory responses are inhibited by ondansetron via central mechanism.[16] Even in studies done by Lakhe G et. Al on 4mg ondansetron[40] and Sagir O et. Al on 3mg granisetron[41], they administered the test drug after giving SA, and found that there was a significant decrease in POS. Since, ramosetron is a newer drug which belongs to the same group of 5HT3R antagonists, we believed that ramosetron would also be useful in the prevention of PSS. Thus, we wanted to determine if the same efficacy of ramosetron will persist, if given immediately after giving spinal anaesthesia.

In a study conducted by Rohit kumar et al. and Kim et al., they witnessed promising results with ramosetron on the prevention of shivering in parturients who were posted for elective caesarean section[3] and in patients who undertook knee arthroscopy under spinal anaesthesia respectively[20]. Ramosetron 0.3mg i.v was given to the patients before inducing spinal anaesthesia and patient has been monitored for shivering. However, the study conducted by Song and Lee proposed no significant anti-shivering role of ramosetron in patients undergoing thyroid surgeries under general anaesthesia.[39] Due to various conflicting results by many researchers, the current study was planned to evaluate the effectiveness of ramosetron as an antishivering agent in patients undergoing infra-umbilical surgeries under neuraxial blockade. Since in the previous studies a dose of 0.3mg ramosetron i.v when used showed successful results, we have planned to use the same dose in our study.

In a study by Fujii Y and Tanaka H, where they compared ramosetron & granisetron for prevention of vomiting in a paediatric population who underwent strabismus surgeries, it showed that almost 85% of patients belonging to the granisetron group (40 μg/kg) were emesis free for 0-24 hours vs 90% with the ramosetron (6 μg/kg) group (P = 0.37); the

corresponding rate 1-2days post anaesthesia was 70% & 95% (P = 0.003) respectively proving that ramosetron is a superior drug for PONV when compared to the other drugs of the serotonin receptor antagonist group.[44] However, there is lack of information on the duration of action of ramosetron for its anti-shivering property post spinal anaesthesia.

This study was directed to compare the effectiveness of ramosetron, a 5HT3 antagonist for the prevention of post spinal shivering in 70 ASA 1 and ASA 2 patients undergoing infra-umbilical surgeries. 35 patients belonged to group A, to whom injection ramosetron 0.3mg i.v was given immediately after spinal anaesthesia. Whereas the remaining 35 patients who belonged to group B received 0.9% normal saline. These patients were monitored for shivering upto a duration of 3hours at intervals of T0, T10, T20, T30, T45, T60, T75, T90, T105, T120, T135, T150, T180 and core body tympanic temperature checked half an hourly.

In our study we did not find any statistically significant difference of demographic values between group A and group B with respect to mean age (42.09 ± 10.34 and 42.9 ± 13.20 years respectively; p value = 0.9177), mean weight (72.71.93 ± 8.14 and 70.43 ± 9.50 kgs respectively; p value = 0.2837) and mean height (168.46±4.68 and 166.63±6.11 cms respectively; p value: 0.1645).

Of the total 35 patients in group A, 10 (28.57%) were female & 25 (71.42%) were male. Of the total 35 patients in group B, 9 (25.71%) were female & 26 (74.28%) were males. On comparison, the difference among the two groups was not found to be statistically significant.

In group A 68.57% patients were ASA grade I and 31.42% were ASA grade II. In group B 57.14% patients were ASA grade I while 14.28% were ASA grade II. The data was comparable in both groups. Therefore, both the groups had similar demographic characteristics.

The temperature of operating room was set constantly at $21^{O}C$. The intravenous fluids which were transfused to the patients were maintained at room temperature. The mean core body temperature of both the group of patients were $98.67^{O}F$ and $98.61^{O}F$ respectively at the baseline, and the difference in core temperature was not statistically significant.

In this study, the data for numerous risk factors of shivering like age, height, weight which determine the level of block, ASA grade and gender were comparable and no statistically significant difference was noted. The temperature of the operating theatre and intravenous fluid have also been maintained at the same temperature for both the groups.

Frank et al. conducted a study on the predictors of hypothermia, which showed that level of spinal block is a substantial predictor of the core body temperature under subarachnoid block. For every increase in the block level, the core body temperature is decreased by $0.15^{o}C$ & for every year of increased age there is 0.03°C reduction in the core body temperature.[13] In our study, no significant statistical difference has been observed in regards to age in both the groups and after giving spinal anaesthesia, maximum sensory level achieved was T6 in all the patients, thereby eliminating any bias which may occur due to these factors. It has been shown that SA reduces the threshold for vasoconstriction and shivering proportionately to the spinal block level. Thus, the sensory block level which is a major factor to cause shivering has been maintained equally in both the groups.

In the present study, we have observed that 9 out of 35 patients had shivering with an incidence of 25.6% in the group A and in group B 21 out of 35 patients were found to have shivering with an incidence of 60%. On comparing both the groups, a p value of less than 0.001 has been obtained which is a highly significant statistical difference.

On comparing the incidences of shivering with studies conducted by Varshney et al. showed a 21% incidence in shivering in group A & 53.8% incidence in the group B (P<0.001). This higher incidence in our study can be attributed to the inclusion of grade 2 or more shivering when present for a duration of 3 or more minutes, where as other studies have included grade 3 or more shivering for giving rescue anti shivering agent.

The onset of shivering in the group B was at 40 minutes and 71.8 minutes in the group A. This difference was observed to be highly significant.

In our study we used tramadol for the treatment of post spinal shivering as Kaya et al., suggested that using i.v tramadol is as equally effective as meperidine, which is the gold standard in the treatment of perioperative shivering.[43] Additionally, the usage of tramadol helps us in avoiding the side effects of meperidine which include sedation and respiratory depression.

The average baseline (before administration of spinal anaesthesia) temperature of patients in the Group A was 98.6^{O}F & in the Group B is 98.6^{O}F. The mean temperature at T0 (at study drug administration) in the Group A is 98.58^{O}F and in the Group B is 98.61^{O}F (P<0110). This difference was found to be significant. However, the mean temperatures which were recorded 30 mins after the induction of spinal anaesthesia was 97.32^{O}F in Group A & 96.5^{O}F in Group B. These observations remained highly significant.

At T60, T90 significant difference in temperature has been observed. At T60 the mean temperature was 97.14 ^{O}F in Group A & 96.96 ^{O}F in Group B (P<0.0156). Further at T90, the mean temperature was 97.21 ^{O}F in Group A & 96.44 ^{O}F in Group B (P<0.0115).

At T120, Group A showed mean temperature of 97.55 ^{O}F and Group B showed 97.83 ^{O}F (P<0.0002), this difference was highly significant. At T150, Group A showed mean temperature of 97.90 ^{O}F and Group B showed 98.14 ^{O}F (P<0.0001) which was highly significant.

At T180, the mean temperature in the Group A was observed to be at 98.24^{O}F and in the Group B at 98.37 ^{O}F with a significant difference (P<0.0289).

Shivering was observed sooner and more extensive in Group B, where 21 out of 35 patients shivered. Out of these 21, shivering was seen as early as at T30 (30mins post spinal) in 10 patients. However, shivering was not observed even in a single patient in the ramosetron group. This difference between the two groups with a P value 0.0011 is very significant. At T45, 1 patient shivered in Group A and 6 patients shivered in Group B. At T60, 2 patients shivered in Group A ad 5 patients shivered in Group B. At T75, the maximum incidence of shivering was recorded in Group A, where 4 patients were shivering in comparison to 0 shivering patients in Group B. At T90, 2 patients shivered in Group A with no incidence in Group B at the given time point.

In our study we observed that the median grade of shivering remained 1 from T30 to T90 in Group B and T60 to T90 in Group A. The occurrence of maximum shivering grade (grade3) at any given time in Group B & Group A was observed to be 34.2% and 8.5% respectively. These findings correlated with study conducted by Badawy et. Al where they found incidence of maximum shivering at any time period was noted to be as 7.8% in ondansetron and 22% in the control group.[17]

The present study has certain limitations such as the number of drapes used and the surface area of the patient exposed to the environment during the surgery varied with the type of surgery. On an average our surgeries lasted for 120 minutes after which the patients were shifted out of the operating room to the post anaesthetic care unit where the room temperature was $25^{O}C$. This led to gradual increase in the body temperature which further decreased the chances of shivering in few patients.

In conclusion, it was found that there was a significant decrease in the incidence of shivering & delayed onset of shivering after spinal anaesthesia in Group A when compared to Group B and also there were no noted adverse effects seen after the administration of ramosetron. The current study included a wide variety of short duration (average-120mins) infra-umbilical surgeries, we have to assess the anti-shivering effect of Inj. Ramosetron 0.3mg i.v in surgeries of longer duration as there will be more chances of developing hypothermia. Further optimization of the dose by evaluating the different doses of ramosetron is needed.

CONCLUSION

In conclusion, there was a significant decrease in incidence of shivering and delayed onset of shivering after spinal anaesthesia in Group A when compared with Group B and also there were no noted adverse effects seen after the administration of 0.3mg Ramosetron.

SUMMARY

Peri-operative shivering is a very frequent complication of subarachnoid block. Shivering leads to an increase in metabolic rate leading to increased oxygen demand and consumption. There is also an increased risk of hypoxemia, lactic acidosis, and catecholamine release. Uncontrolled shivering hinders with the monitoring of vitals in patients and is associated with various perioperative complications especially in high risk patients.

This current study has been conducted to determine the effectiveness of ramosetron 0.3mg i.v. in preventing post spinal shivering in ASA I and II patients. In this study, 70 patients were included. They were divided into 2 groups where Group A (n=35) received 0.3mg i.v ramosetron and Group B (n=35) received 0.9NS i.v. The grade of shivering was periodically assessed in both the groups and the core body temperature was monitored every half hour. Patient having shivering grade 2 or more of Crossley and Mahajan for more than 3 minutes was considered to be shivering. Inj. Tramadol 1mg/kg iv was used to treat shivering and any side effects of ramosetron were noted.

Data was compiled in excel sheet and was subjected to statistical analysis using appropriate tests. The 'p' values were calculated and values < 0.05 were considered to be significant and those less than 0.001 were considered highly significant. Observations were tabulated and statistical significance for intra and intergroup comparison was sought.

In the current study, a highly significant difference has been observed in the incidence of shivering among the two groups. In group A, 25.6% incidence in shivering was observed whereas in group B 60% incidence was observed. The average onset of shivering in group B was at 40 minutes and in group A was at 71.8 minutes. This difference was found to be highly significant.

0.3mg Ramosetron was used in this study without any notable side effects.

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ANNEXURE I

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
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Ref: MDC/DOME/ 174 **Date: 24/12/2019**

To,
BA0119010
PG student in Anaesthesiology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"EFFECTIVENESS OF RAMOSETRON FOR PREVENTION OF SHIVERING IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES UNDER SPINAL ANAESTHESIA – ONE YEAR HOSPITAL BASED, DOUBLE BLINDED RANDOMIZED CLINICAL TRIAL",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE II

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr./Mrs._____ we are requesting you to enroll your ward in study titled **"EFFECTIVENESS OF RAMOSETRON FOR PREVENTION OF SHIVERING IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES UNDER SPINAL ANAESTHESIA – ONE YEAR HOSPITAL BASED, DOUBLE BLINDED RANDOMIZED CLINICAL TRIAL."** conducted by Post Graduate in M.D. Anaesthesiology J.N. Medical College, Belagavi under KLE University, Belagavi.

Respected Sir/Madam We request you allow your ward to participate in our study as he/she is eligible for participating in the study. During the study you will be asked some questions regarding the present complaints that your ward is having.

Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N.Medical College. If you decide to participate you are free to withdraw at any time.

Purpose of the study:

The purpose of research is to know whether ramosetron will be helpful in prevention of shivering in patients undergoing spinal anaesthesia.

Procedure Involved:

If you agree to enroll in my study, I will ask you present, past and family history. Then you will be clinically examined in detail. You will be allotted into one of the two groups randomly using computer generated software. Group A will be given ramosetron for prevention of shivering while Group B will be given normal saline.

Risks: nil

Benefits: Ramosetron is a very potent anti-emetic and also said to prevent shivering.

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enroll your ward in this study. Your decision will not change present or future health care services offered to you or your ward at K.L.E. S Hospital & MRC

Alternatives: Even if you decline the participation in the study, you will get the routine line of management.

Privacy and Confidentiality: The only people to know that you are a research subject is you and the members of the research team. No information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with your identity remaining confidential.

Financial Incentives for participation: No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation: In the event of injury related to the study, treatment will be made available through KLES Hospital and MRC, Belagavi. There is no compensation or payment for such medical treatment by law. If you get injured you may contact Department of Anaesthesiology, KLES Hospital and MRC.

Questions: In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Department of Anaesthesiology, KLES Hospital and MRC, Belagavi or, KLES Hospital and MRC, Belagavi.

If you have any queries about your rights as a study subject, you may call, Department of Paediatrics and Chairman, Institutional Ethical Committee for Human Subjects Research, at J.N. Medical College, Belagavi.

Informed Consent for Participation In Research Trial

"EFFECTIVENESS OF RAMOSETRON FOR PREVENTION OF SHIVERING IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES UNDER SPINAL ANAESTHESIA – ONE YEAR HOSPITAL BASED, DOUBLE BLINDED RANDOMIZED CLINICAL TRIAL.

I, Mr/Ms/Mrs _____ voluntarily agree for the participation of as a subject of study. By signing this consent form, I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name: _____

Guardian Name: _____

Signature or the Left Thumb Print

of Subject/Guardian: _____

Date:

Witness Name: _____ Signature: _____

Investigators Name: _____ Signature:_____

Date:

Place :

ANNEXURE III – PROFORMA

PROFORMA

Title: **"EFFECTIVENESS OF RAMOSETRON FOR PREVENTION OF SHIVERING IN PATIENTS UNDERGOING INFRAUMBILICAL SURGERIES UNDER SPINAL ANAESTHESIA – ONE YEAR HOSPITAL BASED, DOUBLE BLINDED RANDOMIZED CLINICAL TRIAL".**

Patients Name : I.P No. :

Age : Weight :

Height : Gender :

Date of operation : Occupation :

Address : Anaesthesiologist:

Preanaesthetic evaluation

Chief complaints

Past History

Past H/o	Yes	No
Hypertension		
Diabetes Mellitus		
Ishcaemic Heart Disease		
Arrhythmia		
Valvular heart disease		
LVH		
Uncontrolled HTN		
Uncontrolled Diabetes		
Previous surgery		

Family History

General physical examination

Weight (Kg) : Temperature (^{0}F) : Pallor :

Cyanosis : Pedal oedema : Clubbing:

PR : BP: RR:

Systemic examination:

RS: CNS:

CVS: GIT:

Spine -

Investigations

Hb%: Urine routine : FBS:

If patient is above 40years of age

ECG : CXR :

Diagnosis

Proposed surgery

Preoperative physical status ASA Grade I II III IV V

TIME OF (mins)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Spinal					
T0 (study drug)					
T10					
T20					
T30					
T45					
T60					
T75					
T90					
T105					
T120					
T135					
T150					
T165					
T180					

Time of measurement (mins)	Core body temperature
At spinal	
At study drug	
T30	
T60	
T90	
T120	
T150	
T180	

- SIGNATURE OF THE ANAESTHESIOLOGIST: _____
- SIGNATURE OF THE WITTNESS - _____
- SIGNATURE OF THE PRINCIPAL INVESTIGATOR - _____

ANNEXURE IV - PHOTOS

Photo 1: Inj. Ramosetron Hydrochoride

Photo 2: Infrared Tympanic Thermometer

Photo 3: 0.5% (H) Bupivacaine

Photo 4: Measurement of core body temperature

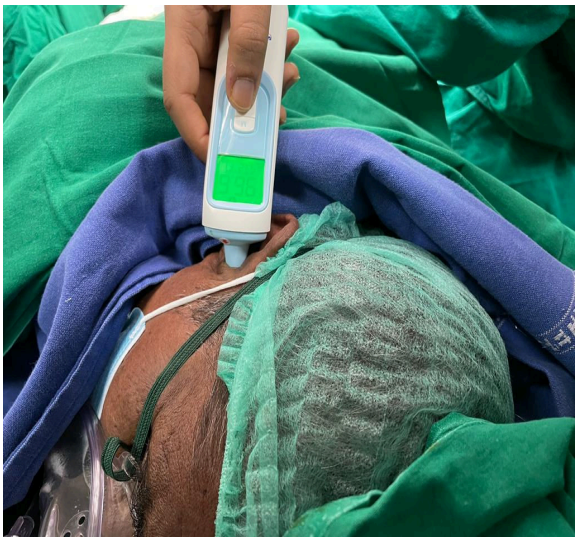

Photo 7: Tramadol

ANNEXURE V- KEY TO MASTERCHART

Yrs	-	years
cms	-	centimeters
Kg	-	Kilograms
ASA	-	American society of anaesthesiology
T	-	Time
Min	-	Minutes
Mg	-	milligram

ANNEXURE -VI

RAMOSETRON																													
S. No.	IP No.	AGE (Yrs)	SEX	HEIGHT (CMs)	WEIGHT (Kg)	ASA	SHIVERING GRADE															SHIVERING ONSET (Min)	TEMPERTURE(DEGREE FAHRENHEIT)								RESCUE TRAMADOL (Mg)
							Tspinal	T_0	T_{10}	T_{20}	T_{30}	T_{45}	T_{60}	T_{75}	T_{90}	T_{105}	T_{120}	T_{135}	T_{150}	T_{165}	T_{180}		Tspinal	T_0	T_{30}	T_{60}	T_{90}	T_{120}	T_{150}	T_{180}	
1	1035786	43	M	168	68	1	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	NIL	98.6	98.6	97.5	97.2	97.4	97.8	98.1	98.5	NIL
2	1001912	20	M	172	70	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	NIL	98.8	98.9	97.4	97.3	97.4	97.5	98	98.41	NIL
3	1001005	37	M	166	68	1	0	0	0	0	0	1	1	1	1	1	0	1	0	0	0	NIL	98.5	98.5	97.4	97.3	97	97.3	97.6	98.1	NIL
4	1024790	26	M	172	74	1	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	NIL	98.7	98.5	98	97.2	97.1	97.4	97.6	98.2	NIL
5	1032290	40	M	176	76	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	NIL	98.7	98.6	98	97.4	97.6	97.9	98.1	98.4	NIL
6	1015019	43	F	164	66	2	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	NIL	98.8	98.7	97.1	96.8	97.2	97.4	97.8	98.2	NIL
7	1037423	36	M	170	75	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	NIL	98.6	98.5	97.5	97.2	97.5	97.6	97.8	98.4	NIL
8	1035397	45	M	178	90	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	NIL	98.8	98.7	97	97.4	97.6	97.8	98.1	98.5	NIL
9	1034719	35	M	175	76	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	NIL	98.6	98.5	97.2	97.1	97.6	97.2	97.8	98.2	NIL
10	1034209	51	M	170	80	1	0	0	0	0	0	2	1	0	0	0	0	0	0	0	0	45	98	97.3	96.6	97					80
11	1034802	40	M	172	88	1	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	NIL	98.7	98.5	97.2	97.3	97.9	98	98.1	98	NIL
12	1034680	48	M	164	78	2	0	0	0	0	0	1	3	1	1	0	0	0	0	0	0	60	98.8	98.6	97.9	96.4					80
13	1034605	40	M	172	72	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	NIL	98.7	98.6	97.3	97.3	97.4	97.8	97.9	98.2	NIL
14	993748	27	M	178	82	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	NIL	98.5	98.5	97	97.3	97.2	97.6	97.8	98	NIL
15	1040226	36	F	163	67	1	0	0	0	0	0	0	1	1	3	1	0	0	0	0	0	90	98.7	98.6	97.2	97.4	97.1				70
16	1040151	34	M	171	72	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	NIL	98.6	98.5	97.4	97.3	97.1	97.8	98	98.2	NIL
17	1033727	48	F	165	70	2	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	NIL	98.6	98.5	97.3	97	97.5	97.9	98	97.9	NIL
18	1032645	60	M	172	75	2	0	0	0	0	0	0	1	2	1	0	0	0	0	0	0	75	98.7	98.5	97	96.9	96.7				80
19	1031956	40	F	163	65	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	NIL	98.8	98.5	97.3	97.2	97.3	97.7	98.1	98.5	NIL
20	1029981	48	M	165	68	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	NIL	98.7	98.7	97.4	97.2	97.3	97.8	97.6	98.2	NIL
21	1032550	41	M	175	78	2	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	NIL	98.8	98.7	97.3	97.1	97.1	97.8	97.9	98.2	NIL
22	1029813	54	M	170	70	2	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	NIL	98.7	98.6	97.8	97	97.2	97.7	97.9	98.1	NIL
23	1031657	55	M	172	85	2	0	0	0	0	0	1	1	3	1	1	1	0	0	0	0	75	98.8	98.7	96.8	96.6	97				85
24	1014217	36	M	164	75	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	NIL	98.7	98.7	97.2	97.4	97.8	97.5	98	98.1	NIL
25	1022685	27	M	167	63	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	NIL	98.6	98.6	97.3	97.5	97.3	97.5	97.9	98.3	NIL
26	992582	60	F	162	58	1	0	0	0	0	0	1	1	2	0	0	0	0	0	0	0	75	98.8	98.8	97.4	97	96.8				60
27	1001586	51	M	168	77	2	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	NIL	98.8	98.8	97.3	97.2	97.4	97.7	98	98.5	NIL
28	1012042	53	F	163	80	2	0	0	0	0	0	0	1	1	2	2	2	1	0	0	0	105	98.8	98.7	97.2	97	96.9	97.1			80
29	1000780	51	M	165	55	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	NIL	98.7	98.6	97.4	97.2	97.1	97.4	98.1	98.4	NIL
30	1023628	45	M	166	78	1	0	0	0	0	0	0	0	2	1	1	0	0	0	0	0	80	98.7	98.7	97.3	97	96.7				80
31	1020632	44	M	168	70	2	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	NIL	98.7	98.6	97.4	97.2	96.9	97.4	98.1	98.5	NIL
32	995496	40	F	166	62	1	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	NIL	98.6	98.5	97.5	97.2	97.1	97.5	97.9	98.2	NIL
33	1024693	60	F	160	84	2	0	0	0	0	0	1	3	1	1	0	0	0	0	0	0	60	98.7	98.6	97.2	97					85
34	1040226	36	F	165	68	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	NIL	98.8	98.8	97.1	97	97.1	97.6	98	98.4	NIL
35	1013356	23	M	169	62	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	NIL	98.5	98.5	97.4	97.2	97.4	97.8	98	98.5	NIL

0.9 NS (PLACEBO)																													
S. No.	AGE (Yrs)	SEX	HEIGHT (CMs)	WEIGHT (Kg)	ASA	TEMPERATURE (DEGREE FAHRENHEAT)															SHIVERING ONSET (Min)	SHIVERING GRADE								RESCUE TRAMADOL (Mg)
						Tspinal	T_0	T_{10}	T_{20}	T_{30}	T_{45}	T_{60}	T_{75}	T_{90}	T_{105}	T_{120}	T_{120}	T_{150}	T_{165}	T_{180}		Tspinal	T_0	T_{30}	T_{60}	T_{90}	T_{120}	T_{150}	T_{180}	
1	22	M	171	65	2	0	0	0	0	1	3	1	1	1	0	0	0	0	0	0	45	98.8	98.7	96.6						70
2	23	M	168	71	1	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	NIL	98.8	98.5	97.2	97	97.2	97.5	98	98.3	NIL
3	53	M	175	80	2	0	0	0	0	0	2	1	1	1	0	0	0	0	0	0	45	98.6	98.4	96.7	96.2					80
4	20	M	165	68	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	NIL	98.5	98.4	97.3	97.1	97.3	97.8	98.1	98.4	NIL
5	20	M	167	74	1	0	0	0	0	0	1	2	1	1	1	0	0	0	0	0	60	98.7	98.5	96.9	96.5	97.1	97.6	98	98.4	80
6	30	M	172	78	1	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	NIL	98.5	98.3	97	96.8	97.2	97.6	98	98.3	NIL
7	58	M	167	70	2	0	0	0	0	0	1	2	1	1	0	0	0	0	0	0	60	98.4	98.3	96.9	96.4					70
8	58	M	169	70	2	0	0	0	0	3	1	1	1	1	1	1	1	0	0	0	30	98.6	98.3	96.8						70
9	35	M	168	65	1	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	NIL	98.6	98.5	97.2	96.9	97.2	97.7	98.2	98.4	NIL
9	49	F	165	61	1	0	0	0	0	0	1	1	1	0	1	1	0	0	0	0	NIL	98.6	98.5	97	97.2	97.5	97.9	98.1	98.3	NIL
11	58	F	176	70	1	0	0	0	0	3	1	1	1	1	0	0	0	0	0	0	30	98.4	98.4	96.7						70
12	45	M	175	75	1	0	0	0	0	1	1	3	1	0	0	0	0	0	0	0	60	98.6	98.2	97.1	96.5					80
13	57	M	170	80	2	0	0	0	1	1	2	1	1	1	0	0	0	0	0	0	45	98.6	98.3	96.9	96.6					80
14	37	M	180	75	2	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	NIL	98.7	98.5	97.1	97.3	97.5	97.9	98.3	98.4	NIL
15	37	F	158	63	1	0	0	0	0	2	1	1	1	1	0	0	0	0	0	0	30	98.5	98.3	96.6	96.9	97.2	97.7	98.2	98.3	70
16	58	M	155	67	2	0	0	0	1	2	1	1	0	0	0	0	0	0	0	0	30	98.6	98.5	96.8						70
17	41	M	170	72	1	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	NIL	98.7	98.6	96.8	97.1	97.3	97.8	98.1	98.4	NIL
18	26	M	162	69	1	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	NIL	98.6	98.5	97.3	97.6	97.9	98	98.3	98.4	NIL
19	45	F	160	65	2	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	NIL	98.4	98.4	96.9	97.2	97.5	97.9	98.2	98.4	NIL
20	54	F	157	70	2	0	0	0	1	1	3	1	1	1	0	0	0	0	0	0	45	98.8	98.6	97.1	96.4					80
21	45	M	170	80	2	0	0	0	0	3	1	1	1	1	0	0	0	0	0	0	30	98.7	98.4	96.6						90
22	45	M	164	85	2	0	0	0	0	1	1	2	1	0	0	0	0	0	0	0	60	98.6	98.2	97	97.3	97.7	98	98.2	98.5	85
23	49	M	172	76	1	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	NIL	98.6	98.6	97.1	97.3	97.6	97.9	98.1	98.4	NIL
24	50	M	168	70	1	0	0	0	0	2	1	1	1	0							30	98.7	98.5	96.6						80
25	60	M	167	68	2	0	0	0	1	3	1	1	1	1	1	0	0	0	0	0	30	98.6	98.4	96.5						70
26	21	F	158	51	1	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	NIL	98.7	98.6	97.2	97.2	97.5	98	98.2	98.5	NIL
27	44	M	159	72	2	0	0	0	0	0	1	3	1	1	0	0	0	0	0	0	45	98.6	98.4	96.9	97					80
28	60	F	160	51	1	0	0	0	0	3	1	1	1								30	98.9	98.7	96.7						60
29	23	M	170	80	1	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	NIL	98.6	98.5	97.3	97.2	97.6	97.9	98.1	98.3	NIL
30	50	F	158	50	1	0	0	0	0	0	3	2	1	1	0	0	0	0	0	0	45	98.4	98.4	97	96.9					60
31	39	M	169	86	1	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	NIL	98.5	98.4	97.2	97	97.4	97.9	98	98.2	NIL
32	51	M	165	55	1	0	0	0	0	0	3	1	1	1	0	0	0	0	0	0	45	98.4	98.4	96.8	96.7					60
33	38	F	163	88	2	0	0	0	0	3	2	1	1	0	0	0	0	0	0	0	30	98.8	98.6	96.6	97					90
34	58	M	175	80	2	0	0	1	1	2	1	1	1	0	0	0	0	0	0	0	35	98.5	98.5	96.7	97.1					90
35	23	F	164	65	1	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	NIL	98.8	98.6	97.3	97.4	97.7	98	98.2	98.4	NIL