"EFFICACY OF DEXMEDETOMIDINE AS AN ANTI SHIVERING AGENT FOLLOWING SPINAL ANAESTHESIA IN ADULTS, A 1 YEAR DOUBLE BLINDED PLACEBO CONTROLLED RANDOMIZED TRIAL"

By

Dr. AVINASH KUMAR JHA
REG NO. BA0112002

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
ANAESTHESIOLOGY

Under the Guidance of

Dr. VANDANA. A. GOGATE **MD,DNB**
Professor

**DEPARTMENT OF ANAESTHESIOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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APRIL - 2015

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I hereby declare that this dissertation entitled **"EFFICACY OF DEXMEDETOMIDINE AS AN ANTI SHIVERING AGENT FOLLOWING SPINAL ANAESTHESIA IN ADULTS, A 1 YEAR DOUBLE BLINDED PLACEBO CONTROLLED RANDOMIZED TRIAL"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. VANDANA. A. GOGATE** **MD,DNB,** Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 590010.

Date:

Place: Belgaum

Dr. AVINASH KUMAR JHA
REG NO. BA0112002

KLE UNIVERSITY, BELGAUM,
KARNATAKA

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Date:

Place: Belgaum

Dr. VANDANA. A. GOGATE MD, DNB
Professor,
Department of Anaesthesiology,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

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Date:
Place: Dr. AVINASH KUMAR JHA

KLE UNIVERSITY, BELGAUM,

KARNATAKA

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Dr. S. N. Suresh **MD,DA**
Professor and Head,
Department of Anaesthesiology,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. (Mrs) Niranjana S Mahantshetti **MD(paed)**
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

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Dr. AVINASH KUMAR JHA
REG NO. BA0112002

ASA – American society of Anaesthesiologists

BMI – Body mass index

cm – Centimeter

CNS – Central nervous system

CO_2 – Carbon dioxide

CVS – Cardiovascular system

ECG – Electrocardiogram

GIT – Gastrointestinal tract

H_2O – Water

Hb – Haemoglobin

Inj. – Injection

IV – Intravenous

Kgs – Kilograms

Mcg – Micrograms

Mg – Milligrams

Min – Minute

Ml – Millilitre

PR – Pulse rate

PAS – Post Anaesthesia Shivering

RBS – Random blood sugar

RR – Respiratory rate

SPO_2 – Saturation percentage of oxygen

α – Alpha

β – Beta

ABSTRACT

Background and objectives

Shivering after spinal anaesthesia is a common complication, which we come across everyday as anaesthesiologists. It is physiologically and emotionally unpleasant for the patient and also makes us think that there is a lacuna in our management. Approximate range of its occurrence is between 5 to 65 % in patients recovering from anaesthesia. The main objective of this study was to assess the efficacy of dexmedetomidine as an anti-shivering agent following spinal anaesthesia in adults.

Methodology:

The study was conducted in the Department of Anaesthesiology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehrunagar, Belgaum in patients undergoing infraumbilical surgeries between January 2013 to December 2013. It was conducted after the approval by the ethical committee and written informed consent was taken from the participants who were to be included in this study. ASA I and II patients in the age group of 18 to 60 years, with the procedure time being at least 45 minutes to 1 hour were included in the study. They were then randomly divided into two groups: Group A (Dexmedetomidine) and Group B (Placebo) using a computer generated table. Tympanic membrane temperature was recorded using infrared thermometer before the start of procedure, after which shivering and sedation were recorded every 15 minutes according to the below mentioned scales:

Shivering was graded on a scale:

0 = no shivering,

1 = piloerection or peripheral vasoconstriction but no visible shivering,

2 = muscular activity in one muscle group,

3 = muscular activity in more than one muscle group but not generalized,

4 = shivering involving the whole body.

Degree of sedation on a 5-point scale:

1 = fully awake and oriented,

2 = drowsy,

3 = eyes closed but open on command,

4 = eyes closed but open to mild physical stimulation,

5= eyes closed and unresponsive to mild physical stimulation.

If greater than grade 3 shivering was observed in any of the groups, rescue drug Tramadol 1mg/kg was given by intravenous route. Any side effects of the drugs were noted.

Results

Our study showed that Dexmedetomidine was effective in prevention of shivering throughout a period of 180 minutes, however the median grades of shivering were insignificant between the two groups after an interval of 150 minutes.

The number of patients receiving Dexmedetomidine who showed no occurrence of shivering were 27 out of 30 (90 %). In the placebo group only 15 out of 30 (50 %) did not experience shivering, anytime throughout the procedure.

Conclusions

Dexmedetomidine 1µg/kg over 20 minutes is a useful drug in prevention of shivering in patients undergoing infra umbilical surgeries under spinal anaesthesia. Dexmedetomidine was found to be effective to combat shivering and can be recommended in prevention of shivering, keeping in mind hypotension and bradycardia as its side effects.

Keywords: Dexmedetomidine, spinal anaesthesia, post anaesthesia shivering, tramadol, thermoregulation

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Chapter 1

INTRODUCTION

Shivering is a protective phenomenon which occurs when there is a drop in the core body temperature. As the patients plunge into anaesthesia, shivering is always bound to happen and its avoidance is of prime importance.

The main control of temperature in the human body is through the hypothalamus, which regulates the body temperature between 36.5 to 37.5 degree Celsius and this is known as the inter threshold range[1]. It is important for the body to maintain this range of temperature for optimal metabolic and physiological functioning and any variations beyond it will lead to derangement of these functions

During any form of anaesthesia there is an imbalance in the body's ability to generate heat as compared to the heat loss.

In general anaesthesia use of inhalational anaesthetics, inhibition of autonomic system and behavioral responses make the patient suffer from hypothermia, whereas in spinal anaesthesia there is a shift of heat to the periphery from the core[2].This shift occurs because of loss of afferent impulses from temperature sensing nerve fibres of the lower half of the body as the spinal nerve roots are blocked by the local anaesthetic, which is injected into the sub arachnoid space

The adverse effects of shivering can lead to increased morbidity. In the process of shivering there is a continuous phase of muscle contractions similar to that of clonus, which leads to anaerobic metabolism, increasing the oxygen consumption and generation of lactate, progressing to metabolic acidosis. According to studies this leads to an elevation in metabolic demands in the range

of 400 to 600 %[3,4]. This can lead to dangerous consequences in coronary artery diseases, pregnancy and other hemodynamically compromised states

Knowing its dangerous effects many non-pharmacological and pharmacological methods have been tried to overcome and prevent shivering from occurring. Non pharmacological methods used are insulators, cutaneous warmers placed beneath the patient, covering the exposed areas using blankets, drapes, use of intravenous fluid warmers. Warm air blowers are also used, but they fail to raise the core body temperature. These methods are usually not sufficient and hence pharmacological treatment is almost always clubbed with the above. The drugs used in the treatment of shivering are: Tramadol, Pethidine nefopam, physostigmine, ketamine, ondansetron, and granisetron[4]. Tramadol in a dose of 1mg/kg has anti shivering action because of its action on central adrenoreceptors, along with inhibition of reuptake of neurotransmitters involved in shivering pathway, but this also associated with significant side effects like nausea and vomiting.

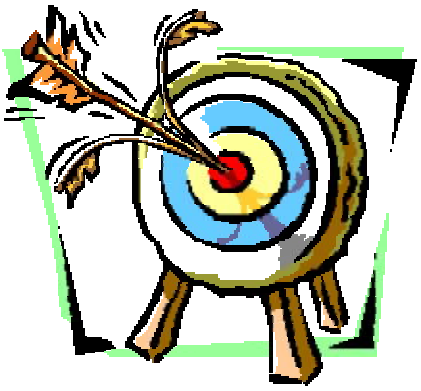
Another drug used was pethidine in the dose of 0.5mg/kg, but considering its opioid properties of respiratory depression, this drug is being replaced by other newer ones. The availability of pethidine is not hassle free and not every setup can procure this drug.

Dexmedetomidine is a α2A adrenergic receptor agonist. It causes hyperpolarization of the noradrenergic receptors leading to decreased firing from the locus ceruleus[5]. This causes analgesia, sedation and also is the possible mechanism in prevention of shivering.

Many trials of dexmedetomidine in prevention of shivering after general anaesthesia have been done, with only a few studies of dexmedetomidine in spinal anaesthesia. More studies are absolutely necessary to show its effectiveness for the same. Thus our attempt through this study was to evaluate the effectiveness of dexmedetomidine in prevention of shivering under spinal anaesthesia.

Chapter 2

Objective



OBJECTIVE

To assess the efficacy of dexmedetomidine in prevention of shivering in adult patients undergoing infraumbilical surgery under spinal anaesthesia.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Spinal anaesthesia is a procedure which is ubiquitous in every healthcare setup. From the day it was described by August Bier in 1898[6], this technique has undergone many modifications with time. The management of its complications have also undergone many changes with the constant research in this area, to make it more safer and acceptable to the patient.

One of the complications which still haunts the anaesthesiologists and thus needs further modifications in its management is shivering. It is not an uncommon scene to see a patient shiver and complain about being uncomfortable. It can be either an intra operative event or a post operative event.

It was Santorio in 1646 who discovered clinical utility of monitoring temperature. After which Wunderlich stressed on its importance[3]. Since then many methods have been suggested for monitoring temperature to help us know the occurrence of shivering during general anesthesia and regional anesthesia. Many non-pharmacological methods and pharmacological drugs have been tried to treat shivering, but even today there are many lacunae with respect to its management. When put into clinical use, we understand that an ideal way of managing shivering is still lacking.

Many comparisons have been made between the different drugs used for the treatment of shivering which are said to possess anti shivering properties during intra operative and post operative periods[7,8]

Incidence of shivering with perioperative dexmedetomidine in 80 patients undergoing general anesthesia for laparoscopic surgeries was studied. Out of these, 40 patients received Dexmedetomidine 1µg/kg in 2 ml saline over 10 minutes, 30 minutes before the end of the surgery. The rest 40 patients received same volume of saline over 10 minutes. There was significant difference in the grades of shivering ($P < 0.05$) between the two groups. Thus dexmedetomidine seemed to have antishivering effect in a dose of 1µg/kg. However patients also had dry mouth and sedation, probably a side effect of dexmedetomidine.[9]

In another study, efficacy of alpha 2 agonist Dexmedetomidine in prevention of shivering was studied in 70 patients undergoing surgery under general anaesthesia. Dexmedetomidine 1µg/kg or normal saline were given over 10 minutes, 20 minutes before the end of the procedure. It was found that shivering was of grade 0 in 88.5 % in the dexmedetomidine group of grade 0 in 54 % of patients in the saline group. Hence it was concluded that dexmedetomidine 1µg/kg was safe and effective in prevention of post operative shivering[10].

A study was done to evaluate the effect of dexmedetomidine on shivering during spinal anesthesia. Of the 60 patients selected, 30 patients were administered 0.9% normal saline and the other 30 patients were given Dexmedetomidine at 1 µg/kg over 10 minutes, followed by 0.4 µg/kg/hour until skin incision. Their results showed that the occurrence of shivering in dexmedetomidine group was only 10 %, compared to the 0.9% normal saline, where it was 56.4%[11]

Another study was conducted where they hypothesized that in children with postanesthesia shivering would reduce shivering behavior following a single bolus dose of dexmedetomidine, 24 children ranging in age from 7 to 16 years (11.5 ± 2.5 years) were treated. All children had a cessation of shivering behavior within 5 min following the completion of dexmedetomidine administration[12]

Efficacy of Dexmedetomidine and meperdine was studied, where a comparison was made between dexmedetomidine 1µg/kg with meperidine 0.5mg/kg and 0.9% saline as placebo in 120 patients for their action on prevention of post anaesthetic shivering in elective abdominal or orthopaedic surgeries under General anaesthesia. Results showed that both Dexmedetomidine 1µg/kg and 0.5mg/kg pethidine were useful in prevention of shivering and there was no statistically significant difference between them.[13]

Another study mentioned that during wound closure for procedures under General Anaesthesia, Dexmedetomidine successfully reduced the shivering threshold and vasoconstriction threshold in healthy volunteers. Dexmedetomidine (1 µg/kg) given at the time of wound closure significantly reduced postanesthesia shivering compared to patients who received saline [15% vs. 55%, respectively] and was comparable to meperidine 0.5 mg/kg (10%).Compared to the control group (saline), dexmedetomidine and meperidine significantly lowered the shivering threshold by 0.7 degree Celsius and 1.2 degree Celsius, respectively. And they also concluded that this agent deserves further study for its utility in the clinical setting of moderate hypothermia.[14]

Dexmedetomidine was evaluated for its effects on shivering in women undergoing elective hysterectomies. 90 ASA I and II were included in the study and were divided into two groups of dexmedetomidine and placebo, of 45 each. Dexmedetomidine was administered as a loading dose of 1µg/kg over 10 minutes, followed by a maintenance infusion of 0.4µg/kg/hour. They found that only 7 out of 45 patients in the dexmedetomidine group experienced shivering, Ramsay sedation score was also found to be higher in the dexmedetomidine group over the first hour.[15]

Another study was conducted on evaluation of optimal dose of dexmedetomidine versus 0.9 % normal saline in the prevention of post anaesthesia shivering in 130 patients. They used 3 doses of dexmedetomidine which were 0.5, 0.75, 1 µg/kg in 3 different groups. They concluded that groups of 0.75 and 1 µg/kg had lesser incidence of shivering and lesser requirement of rescue drug.[16]

Effects of preemptive tramadol and dexmedetomidine for their ability in prevention of shivering during arthroscopy was studied. Of the total 90 patients, 30 received 100 mg tramadol in 100 ml saline in group T- (n = 30) and 0.5 µg/kg dexmedetomidine in 100 ml saline in group D - (n = 30) and 100 ml saline was administered in group P - (n = 30) in 10 min. It was found that both the Dexmedetomidine and the tramadol group were useful in prevention of shivering following spinal anaesthesia, and that dexmedetomidine group had better sedation scores.[17]

Another double blinded comparative study of tramadol and dexmedetomidine for post spinal anaesthesia shivering was conducted, in which 50 patients were randomized in two groups of 25 patients each to receive either dexmedetomidine 0.5 µg/kg or tramadol 0.5 mg/kg as a slow intravenous bolus (diluted to a volume of 5 ml in a 5 ml syringe) . They observed that time taken for cessation of shivering was significantly less with dexmedetomidine when compared to tramadol. Nausea and vomiting was observed only in tramadol group (28% and; 20% respectively). Thus, they concluded that although both drugs are effective, the time taken for cessation of shivering is less with dexmedetomidine when compared to tramadol. Moreover, dexmedetomidine has negligible adverse effects, whereas tramadol is associated with significant nausea and vomiting.[18]

With all these studies showing a definite role of dexmedetomidine in management of shivering, more studies are necessary for delineating the appropriate dose, other beneficial and adverse effects of this drug.

Chapter 4

Basic Sciences

BASIC SCIENCES

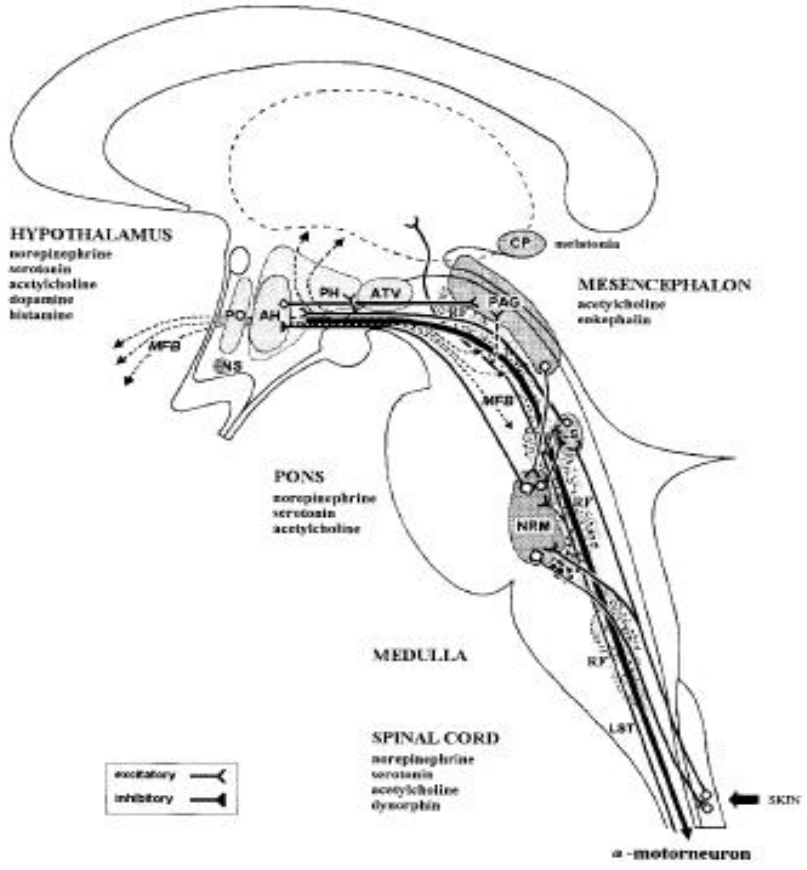
Normal Body Temperature Regulation

Like the blood pressure and heart rate, there is a tight regulation of body temperature. The control system is complex and involves both positive and negative-feedback systems that are so widely distributed that nearly every part of the autonomic nervous system contributes to some extent.

By 1912, physiologists recognized the dominant thermoregulatory site in mammals to be the hypothalamus, because control was markedly compromised by injury or destruction of the hypothalamus.

Considerable pre-processing of thermal information occurs, as it traverses from peripheral to central tissues.[19] The processing of thermoregulatory information occurs in three phases:

- Afferent thermal sensing
- Central regulation
- Efferent responses



Afferent Input—Majority of the physiologic processes are temperature dependent, specific cells are markedly activated or inhibited by thermal perturbations.

The temperature sensor cells can be divided into

- Warm sensing cells
- Cold sensing cells.

Cutaneous thermo reception is better understood as it is more easily accessible, and thus understood in a better way.[20] Human skin is highly sensitive to temperature: An increase in forehead temperature of as little as 0.003°C can be detected. The skin is more sensitive to rapid thermal changes than to those occurring slowly.

Cold signals are carried from the skin primarily by *via* A∂ nerve fibers whereas warm signals are carried by unmyelinated C fibers.[21] Until now, little was known about how the temperature change is detected by these fibers.

However, it appears that Transient Receptor Potential (TRP), vanilloid (V) and menthol (M) receptors may be the fundamental temperature sensing elements both in skin and the dorsal root ganglia. These receptors have a high temperature sensitivity.

Most ascending thermal information traverses the spino-thalamic tracts in the anterior part of spinal cord, but no single spinal tract is critical for conveying thermal information. Consequently, the entire anterior cord must be destroyed to ablate thermoregulatory responses.

The hypothalamus, spinal cord, deep abdominal and thoracic tissues, and the skin surface each contribute around 20 percent of the total thermal input to the central regulatory system.[22,23] Hence although the hypothalamus is the dominant thermoregulatory controller, its temperature per se is not especially important

Central Control—The most simple model of thermoregulation is the "set-point" system in which all thermoregulatory responses are simultaneously turned on or off in response to hypothalamic temperature. This is an inadequate representation of the thermoregulatory system because:

- responses are determined by thermal input from nearly every portion of the body;
- responses do not occur simultaneously or at similar temperatures;
- this model does not incorporate a "null zone" in which no thermoregulatory responses occur; and
- This model cannot explain thermal adaptation and a host of other observed phenomena.

The General Thermoregulatory Model— In this model there is integration of thermal input from tissues throughout the body at variety of centers (including the spinal cord and brain stem), but most importantly the hypothalamus.

Temperature is regulated by central structures that compare integrated thermal inputs from the skin surface, neuraxis, and deep tissues with thresholds for each thermoregulatory response. Control is distributed in the sense that thermal input is integrated at various levels within the neuraxis, but the dominant controller in mammals is the hypothalamus. Similarly some thermoregulatory responses can be mounted only by the spinal cord.[23] For example, animals and patients with high spinal-cord transections regulate temperature much worse than normal — but are not poikilothermic.

The slope of response intensity versus core temperature defines the *gain* of a thermoregulatory response. The *maximum intensity* of the response is defined as when response intensity no longer increases with further deviation in core temperature. There is only background insensible water loss from the skin without anesthesia until the threshold is reached at a core temperature of 36.5°C.

The sweating rate then increases quickly as core temperature increases an

additional 0.5°C (gain), but remains essentially constant with further hypothermia (maximum response intensity). Although the threshold increases as a function of isoflurane concentration, during anesthesia the gain and maximum intensity remain similar.[24]

Approximately 80 percent control of autonomic responses is determined by thermal input from core structures[25,26] and remains similar during anesthesia Normal core temperatures in humans typically range from 36.5°C to 37.5°C; values <36°C or >38°C usually indicate loss of control or a thermal environment at a level where it overcomes thermoregulatory defenses.

Thermoregulatory modeling is thus complicated by interactions with other regulatory responses and time-dependent effects.

Most thermoregulatory models do not adequately account for the rate at which central and peripheral temperatures change. Consequently, they should be applied to vigorously dynamic situations with caution. Similarly, at least under some circumstances thermoregulatory responses are not determined only by instantaneous thermal inputs, but instead reflect the recent history of thermal perturbations. The extent to which time and temperature-dependent factors contribute to human thermoregulatory responses remains unclear.

Thresholds— It is not fully understood how the body determines absolute threshold temperatures, perhaps it involves inhibitory postsynaptic potentials in hypothalamic neurons[27] which are modulated by

- norepinephrine,
- dopamine,
- 5-hydroxytryptamine,
- acetylcholine,
- prostaglandin E1, and
- neuropeptides.

The thresholds vary daily by 0.5−1°C in both sexes (circadian rhythm)[28]and by ≈ 0.5°C with menstrual cycles in women.[29]

Exercise, nutrition, infection, hypo- and hyperthyroidism, drugs (including alcohol, sedatives, and nicotine), and cold- and warm-adaptation all alter threshold temperatures. But each of these effects is small compared to the profound impairment induced by general anesthesia.

The *interthreshold range* (core temperatures *not* triggering autonomic thermoregulatory responses) is bounded by the sweating threshold at its upper end and by the vasoconstriction threshold at the lower end. Within this range, temperatures are presumably sensed accurately but do not trigger regulatory responses.

In humans the interthreshold range is usually only 0.2−0.4°C.[30] and this range defines normal body temperature. Both sweating and vasoconstriction thresholds are 0.3−0.5°C higher in women than men. Central thermoregulatory control is presumably immature in less-developed infants such as those weighing less than a kilogram.

This regulation appears consistently normal in people aged less than 80 years.[31]

Efferent Responses— responses to temperature changes beyond the threshold range include sweating, peripheral cutaneous vasoconstriction, and brown fat metabolism. Adaptation of pre-existing systems for thermoregulatory control is consistent with the hierarchical thermoregulatory model proposed by Satinoff[19] and this explains why thermoregulatory control is so widely disbursed. Thermal perturbations, (defined by body temperature difference from a specific threshold) triggers effector responses that actually mediate appropriate increases in environmental heat loss or increases in metabolic heat production. Each response has its own threshold and gain.

Thus the control system is able to activate responses in an efficient order (i.e., vasoconstriction before shivering) and only to the extent actually necessary to maintain core temperature.

i.Behavioral Regulation— this is the most powerful thermoregulatory effector and this modification allows humans to live in the warmest and coldest climates on earth behavioral responses play an important role when autonomic thermoregulatory responses are insufficient for maintaining central temperature. Most commonly this involves simple manoeuvres such as moving from direct sun into shade, dressing more warmly, or altering ambient temperature using a heating/air conditioning system. Behavioral responses require a conscious perception of body temperature.

ii.Vasomotion—most consistently used autonomic effector mechanism to reduce heat loss is cutaneous vasoconstriction. Total digital skin blood flow is divided

into nutritional (mostly capillary) and thermoregulatory (mostly arterio-venous shunt) components.[32]

Arterio-venous shunt flow tends to be “on” or “off” which is simply a way of saying that the gain of this response is high. Around 10 percent of cardiac output traverses arterio-venous shunts; consequently, shunt vasoconstriction increases mean arterial pressure ≈15 mmHg.[33]

These shunts are located only in acral regions (fingers, toes, nose, etc.). These specialized thermoregulatory vessels are under alpha adrenergic control and are constricted by norepinephrine released from sympathetic nerves and and appear to be almost exclusively controlled by central thermoregulatory status

iii.Non-shivering Thermogenesis—Non-shivering thermogenesis is defined as an increase in metabolic heat production not associated with muscular activity. This increase occurs largely in specialized fat called brown adipose tissue located largely in the intrascapular and perirenal areas and this tissue has the highest metabolic rate of any organ. Brown fat has a dark hue because it is loaded with mitochondria. When stimulated by norepinephrine released from sympathetic nerves, mitochondrial respiration in brown ATPase tissue proceeds normally. However, production of ATP is prevented by an “uncoupling protein” which allow protons to reenter the sarcoplasmic reticulum without driving the sodium-potassium ATPase.[34]

Nonshivering thermogenesis is the primary defense against cold and can easily double or triple metabolic heat production (measured as whole-body

oxygen consumption) without producing mechanical work. Nonshivering thermogenesis also doubles heat production in infants.

In adult humans, non-shivering thermogenesis is poorly developed and contributes little to thermal balance in adult humans.[35]

iv.Shivering—Sustained shivering augments metabolic heat production 50 to 100 percent in adults. This increase is small compared with that produced by exercise (which can increase metabolism five-fold) and is, thus, surprisingly ineffective. Shivering is manifested as an irregular tremor which on electromyographic analysis consists of randomly overlapping myofibril depolarization spikes.

Superimposed on this rapid and apparently disorganized local activity, is a 4 - 10 cycles/minute waxing-and-waning activity. Notably, this slow amplitude modulation is synchronous and occurs simultaneously in all muscles throughout the body.[36] Shivering does not occur in newborn infants and probably is not fully effective until children are several years old.

v.Sweating—Sweating is mediated by post-ganglionic, cholinergic nerves. It is an active process that is prevented by nerve block or atropine administration. Each gram of evaporated sweat dissipates 0.58 kcal.

During heat stress, active dilation of pre-capillary arterials increases capillary blood flow enormously.

This dilation involves withdrawal of tonic sympathetic stimulation and most likely involves release of unknown factors from sweat glands; the mediator may be nitric oxide or neuropeptide Y.[37] The threshold for active vasodilation usually is similar to the sweating threshold, but maximum cutaneous vasodilation is usually delayed until sweating intensity is at its maximum.

Thermoregulation During Neuraxial Anesthesia

Neuraxial anesthesia impairs the Central thermoregulatory control, but this is combined with reduced gain and maximum response intensity of shivering. Autonomic impairment is compounded by an impairment of behavioral regulation so that patients do not recognize that they are hypothermic. And added to this, regular monitoring of core temperature is not done during neuraxial anesthesia. This leads to a condition where neither the patient nor the anaesthesiologist sense hypothermia.

Response Thresholds

Both epidural and spinal anesthesia reduce the thresholds of triggering vasoconstriction and shivering by about 0.6°C. Although the magnitude is less, the pattern of impairment is thus similar to that observed with general anesthetics and opioids, most likely suggesting an alteration in central, rather than peripheral control. The mechanism by which peripheral administration of local anesthesia impairs centrally mediated thermoregulation remains unknown, but is proportional to the number of spinal segments blocked.[38]

During regional anesthesia, core hypothermia is accompanied by a real increase in skin temperature. The paradoxical result is often a perception of continued or increased warmth, accompanied by autonomic thermoregulatory responses including shivering.[39,40]

Shivering During Neuraxial Anesthesia

Shivering-like tremor is common during neuraxial anesthesia and has mainly four etiologies:

1) normal thermoregulatory shivering in response to core hypothermia;
2) normal shivering in normothermic or even hyperthermic patients who are developing a fever;
3) direct stimulation of cold receptors in the neuraxis by injected local anesthetic; and,
4) nonthermoregulatory muscular activity that resembles thermoregulatory shivering.

Other etiologies remain possible. For example, shivering that occurs immediately after induction of spinal or epidural anesthesia for cesarean delivery — well before a decrease in core temperature, for which the cause is yet to be identified. Electromyographic analysis of normal shivering shows that a tremor has the 4-8 cycles/minute of waxing-and-waning pattern.[41] Fever is defined by a regulated increase in thermoregulatory response thresholds and can thus provoke shivering even in normothermic individuals.

Not all shivering-like tremor is thermoregulatory. It is possible to detect low-intensity shivering-like muscular activity in both surgical patients and during labor. The cause of this muscular activity remains unknown, but it is associated with pain and may thus result from sympathetic nervous system activation.[42] Since skin temperature contributes to control of thermoregulatory responses, shivering of any type can be treated by warming the skin surface[43].

This is why shivering so often stops in a matter of seconds after entering a warm room even though core temperature has not changed at all. However, the entire skin surface contributes 20% to thermoregulatory control and the lower body contributes about 10%, sentient skin warming is likely to only compensate for small reductions in core temperature. As might thus be expected, skin warming is only effective in a fraction of patients.

Most often, pharmacologic treatments will be required for moderate or severe shivering. The same drugs that are effective for shivering after general anesthesia can be used to treat shivering during neuraxial anesthesia: these include

- meperidine (25 mg, IV or epidurally),[44]
- clonidine (75 μg, IV),[45]
- ketanserin (10 mg, IV)[45]and
- magnesium sulfate (30 mg/kg, IV).[46]

Responses in Infants and the Elderly

Thermoregulatory control is profoundly impaired by most any type of general anesthesia in adults, resulting in a wide interthreshold range between 2-4°C, over which core temperature variation fail to trigger regulatory defenses. Thermoregulatory control in anesthetized infants and children, is similar to that of adults. For example, thermoregulatory vasoconstriction is comparably impaired in infants, children, and adults given halothane[47] or isoflurane.[48] In contrast, the vasoconstriction threshold is about 1°C less in patients aged 60-80 years than in those between 30 and 50 years old.[49,50] Infants are thus at a greater

risk of hypothermia because the large surface area-to-mass ratio increases the relative difference between heat loss to heat production.

Nonshivering thermogenesis is an important thermoregulatory response in infants. However, it fails to increase the metabolic rate in infants anesthetized with propofol.[51] Thus, it appears that nonshivering thermogenesis is relatively unimportant in perioperative patients and certainly has a small effect compared with the approximately 30% reduction in metabolic rate associated with general anesthesia

PERIOPERATIVE TEMPERATURE MONITORING

Temperature monitoring is a vital aspect of perioperative monitoring. A number of devices have been used for the same purpose. The type of transducer used and the site of monitoring may be different. Tranducers commonly used in clincical practice are thermocouples, thermistors and infra red emission thermometers. These infrared thermometers are called as tympanic membrane thermometers. The single best indicator of body temperature is Core body temperature.[52,53,54]

Core body temperature monitoring is appropriate for most patients undergoing general anesthesia, to detect the occurrence of hypothermia, hyperthermia,[52] malignant hyperthermia. This aspect of temperature monitoring is seldom evident in patients undergoing regional anesthesia. Thus a significant hypothermia is often undetected in many patients.[53]

SITES OF MONITORING

Axillary temperature:

They are relatively close to core body temperature and may be reasonable in selected patients.[52]

Oesophageal temperature:

It is monitors with a thermistor or thermocouple incorporated into a oesophageal sthetoscope. It gives accurate readings of core body temperature in all conditions.[52]

Nasopharyngeal temperature:

Measured by placing the oesophageal probe positioned above the palate, it is reasonably close to brain and core body temperature.[52]

Bladder Temperature:

Measured with a Foleys catheter with an attached thermistor or thermocouple. Even though, it is a close approximation of core body temperature, its accuracy decreases in lower abdominal procedures and states of low urine output.[52]

Infrared ear and tympanic membrane thermometers:

These are based on the principle the all objects emit electromagnetic radiation over a wide range of wavelengths. Intensity of this radiation and wavelength for which the intensity of emitted radiation is maximum depends 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.[52]

Disadvantages with this mode of temperature monitoring are:

- Intermittent measurement
- Poor penetration and obstruction due to impacted wax
- Associated perforation of the ear canal can be a problem[52,53]

Monitoring of the vital signs and temperature during the surgery are essential. By doing this we can prevent hypothermia and its associated complications like patient discomfort, cardiac morbidity, wound infection, and surgical bleeding[54]

DRUGS USED FOR SHIVERING

Feldberg and Myers came up with a theory on thermoregulation in 1963. It said that temperature set point in the body was done by a balance between norepinephrine and serotonin in the pre-optic anterior hypothalamus.

- Serotonin causes vasoconstriction and shivering leading to concomitant increase in core temperature
- Norepinephrine and epinephrine lower the resting body temperature and attenuate serotonin induced hyperthermia

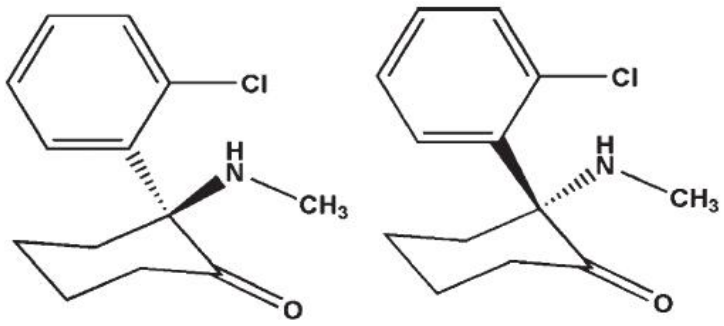
Further anti shivering agents belong to several different classes of drugs namely cations, endogenous peptides, biogenic amines, NMDA receptor antagonists.[55,56,57,58]

KETAMINE:

Ketamine Hydrochloride is a phencyclidine derivative that produces Dissociative anaesthesia. It is known to produce cataleptic state in which the subject the subject is separated from the surrounding. It renders the patient non communicative, even though wakefulness may be present.

STRUCTURE

Ketamine is a chiral compound and it contains two optical isomers or enantiomers. Most preparations of ketamine are racemic which contain both enantiomers (+) and (-) in equal amounts.



R-(–)- ketamine *S*-(+)- ketamine

AVAILABILITY

Available as a 10 ml Vial and 2ml ampoule

MECHANISM

Ketamine is a potent anaesthetic agent. It produces "Dissociative Anaesthesia" where it stimulates the thalamic and the limbic system and inhibits medial medullary reticular formation causing functional and electrophysiological dissociation between thalamus and limbic system. It is a potent analgesic at sub anaesthetic doses and action is mediated by various receptors namely NMDA, GABA, Voltage gated Na and K channels. Ketamine binds competitively to N-Methyl-D-Aspartate (NMDA) receptors, which is implicated in modulation of central thermoregulatory centres for shivering.

In addition, Ketamine may exert effects at other sites including opioid receptors, monoaminergic receptors, and voltage sensitive sodium and L type calcium channels.[54]

Metabolism

It is metabolised by the hepatic microsomal enzymes. The major pathway involves demethylation to form norketamine. Which is then hydroxylated to hydroxyketamine. These products are conjugated to water soluble glucoronide derivatives and are excreted in urine.

ROUTES

Ketamine can be given by intravenous, intramuscular, subcutaneous, oral, rectal, nasal, transdermal, epidural, intrathecal routes

DOSAGES:

1. **Induction of General Anaesthesia**

   0.5 – 2 mg/kg IV

   4-6 mg/kg IM

2. **Maintainence of Gerneral Anesthesia**

   0.5- 1 mg/kg IV with 50% N20 in o2

   15- 45 micro.gram/kg/min with 50%-70% N20 in o2

3. **Sedation and Analgesia**

   0.2-0.8 mg/kg IV over 2-3 minutes

   2-4 mg/kg IM

USES

1. Pediatric anesthesia- As a sole anaesthetic for minor procedures or as an induction agent.
2. Asthmatics or patients with chronic obstructive airway disease.
3. In emergency medicine in entrapped patients suffering from severe trauma.
4. To supplement spinal/ epidural anesthesia/ analgesia utilizing low doses.
5. Small doses(0.1-0.5 mg/kg) as a local anaesthetic, particularly for the treatment of pain associated with movement and neuropathic pain.
6. As a co-analgesic, it is most effective when used alongside a low-dose opioid.

SIDE EFFECTS

1. Hallucinations
2. Dizziness
3. Light Headedness
4. Nausea
5. Emergence Delirium
6. Excessive Salivation
7. Increased sympathetic response- increased Blood pressure, heart rate, cardiac output.

TRAMADOL

Tramadol Hydrochloride is a centrally acting analgesic drug, it possesses agonist actions at the mu opioid receptors and also affects reuptake of noradrenaline and serotonin.

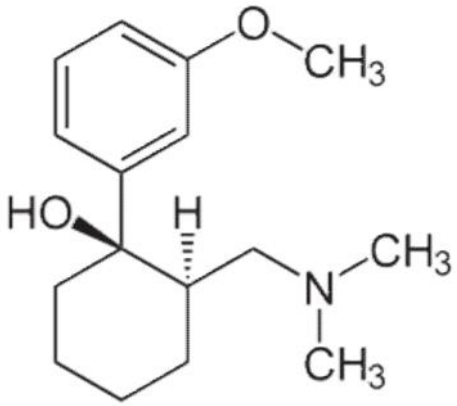
STRUCTURE

It is a synthetic piperidine analog of the phenantherane alkaloid Codeine. It is an opioid- chemicals which act upon one or more of the human opiate receptors, mu 1 and 2 receptors. The opioid agonistic effect of Tramadol and its major metabolites are almost exclusively mediated by the substance's action at the mu receptor. This characteristic distinguishes Tramadol from many other substances of the opioid drug class, which generally do not possess Tramadol's degree of subtype selectivity. It is converted to O- desmethyltramadol which is also responsible for its stereoselective analgesic effect.[4,56,64,65]

STEREOISOMERS

Tramadol [2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol] has two stereogenic centres at the cyclohexane ring. Thus, it may exist in four different configurational forms:

- (1R,2R)-isomer
- (1S,2S)-isomer
- (1R,2S)-isomer
- (1S,2R)-isomer



AVAILABILITY

Marketed as the hydrochloride salt. Available as IV(Intravenous), IM(Intramuscular) and oral administration.[66,67,68,69]

MECHANISM OF ACTION

Tramadol acts as a mu opioid receptor agonist, serotonin releasing agent, norepinephrine reuptake inhibitor, NMDA receptor antagonist, nicotinic antagonist, nicotinic acetylcholine receptor antagonist, and M1 and M3 muscarinic acetylcholine receptor antagonist

The analgesic action of tramadol has yet to be fully understood but it is believed to work through modulation of serotonin and norepinephrine in addition to its mild agonism of the mu opioid receptor.

It inhibits reuptake of neurotransmitters which play an important role in the pathway of shivering. It is a potent inhibitor of reuptake of serotonin, norepinephrine and dopamine at the synaptic junction. It also facilitates the release of serotonin. It reduces the neuronal firing rate and hyperpolarizes neurons in concentration dependent manner in the locus coeruleus. Locus coeruleus appears to be pro shivering centre that activates heat production. It is also the main noradrenergic nucleus involved in the descending pain control system, which is regulated by serotonin.

Another centre in the brainstem, dorsal raphe nucleus possesses antishivering action which inhibits thermogenesis. A significant amount of norepinephrine exists in nucleus raphe magnus.[59,66,67,68,70,71]

USES

1. Diabetic neuropathy
2. Post herpetic neuralgia
3. Fibromyalgia
4. Restless leg syndrome
5. Opiate withdrawal syndrome
6. Migraine headache
7. Obsessive compulsive disorder
8. Premature ejaculation

SIDE EFFECTS

1. Nausea, Vomitting
2. Memory loss
3. Sweating
4. Constipation
5. Drowsiness

DRUG INTERACTIONS

1. Respiratory depression is a common side effect of most opioid, not commonly seen with tramadol
2. Decrease in seizure threshold when used in patients on SSRI, TCA, or patients with epilepsy
3. Dose of Warfarin may need to be reduced for anticoagulated patients to avoid the complication of bleeding

METABOLISM

It is metabolized by hepatic cytochrome P450 enzyme system to a major metabolite o- Desmethyltramadol. It is significant as it has 200 times the mu affinity of tramadol and has an elimination half life of nine hours, compared to six hours of tramadol itself. In the 6% of population that have slow CYP2D6 activity, there is therefore slightly reduced analgesic effect. Phase II hepatic metabolism renders the metabolites water- soluble, which are excreted by the kidneys. Thus, reduced doses may be used in renal and hepatic impairment.[66,67,68,69]

PETHIDINE

It is the only opioid which has anti shivering property, which is one amongst its several non opioid actions. It produces considerable inhibition of serotonin reuptake in analgesic concentrations. It also possesses non competitive NMDA receptor antagonist activity in the spinal cord. In addition it has anticholinergic effects.

An important contribution made by Takda Et al showed that pethidine can bind to alpha 2- adrenoreceptors subtype and transduce an agonist action at these sites. These actions are responsible for the anti shivering actions in the locus coeruleus.

Pethidine thus possesses anti shivering properties that are not shared by pure mu receptor opioids. The drugs antishivering properties may simply result from the drug's lack of specificity and a fortunate accumulation of pharmacologic actions modulating thermoregulatory shivering.[3,59,60,61,62,63]

MISCELLANEOUS DRUGS

Other drugs which possess antishivering actions-

Nefopam is an analgesic drug with powerful anti shivering property. It is a potent inhibitor of synaptosomal uptake of serotonin, norepinephrine, and dopamine, and slightly lowers the body temperature[1,2,3]. It is an antihypertensive drug which is an antagonist of both 5-HT2 receptors and a1- adrenoreceptors. It acts indirectly via facilitation of a central presynaptic a2- adrenoreceptor mechanism in the lower brainstem[1,2,3].

Ondansetron and Granisetron. 5 HT-3 receptor antagonists, known for their antiemetic actions, are currently under investigation for a possible role in prevention and treatment of postanaesthetic shivering.[1,2,3,56]

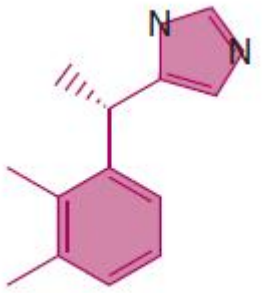
Physostigmine is effecetive in prevention of post anaesthesia shivering. Physostigmine is a non-selective centrally acting cholinesterase inhibitor. Its analgesic effect are mediated by cerebral cholinergic muscarinic receptors, but serotoninergic receptors and an endorphinergic mechanism may also be involved. Analgesia after intrathecal administration of anticholinesterase is mediated through muscarinic receptors. There is is also a known synergistic interaction with the intrathecal mu opioid and a2 adrenergic agonist receptor, which mediate thermoregulatory effects and are still under study.[1,2,3,56,57,58]

Calcium (Ca2+) and **Sodium(Na+)** play a functionally opposing role in mediation of body temperature. Excess of Ca2+ into the posterior hypothalamus leads to a decrease in the body temperature while excess of Na+ increases the body temperature. The magnitude of this response depends on the ratio of cations concentration and may thus define the " setpoint" for body temperature[1,2,3].

Magnesium is a physiologic antagonist of NMDA receptor and was found to stop post anaesthetic shivering. The possible role in cold adaptation is due to decrease in the threshold of post anaesthetic shivering[1,2,3].

Methylphenidate is effective for prevention and treatment of postanaesthetic shivering. It is an analeptic agent that binds presynaptic sites on dopamine, norepinephrine and 5-HTtransport complexes, which in turn block reuptake of respective neurotransmitters. Activation of the raphe system and the concomitant arousal may explain the impressive anti-shivering potency of methylphenidate. However, experimental evidence for the precise anatomical substrate of methylphenidate's anti shivering action is lacking.[1,2,3,56,57,58]

DEXMEDETOMIDINE: is a highly selective, specific, and potent alpha adrenergic agonist (1,620:1 alpha2 to alpha1) This drug is the dextroisomer and pharmacologically active component of medetomidine, which has been used for many years in veterinary practice for its hypnotic, sedative, and analgesic effects. Compared with clonidine, dexmedetomidine is seven to ten times more selective for alpha2 receptors and has a shorter duration of action than clonidine. Atipamezole is a specific and selective alpha2 receptor antagonist that rapidly and effectively reverses the sedative and cardiovascular effects of IV dexmedetomidine



Dexmedetomidine

Mechanism of Action:

Acts on the alpha 2A receptors in CNS causing hyperpolarization via K^+ influx. This leads to decreased neuronal firing and reduced norepinephrine release Causing anxiolysis, sedation, anti shivering action.

Pharmacokinetics

The elimination half-time of dexmedetomidine is 2 to 3 hours compared with 6 to 10 hours for clonidine. Dexmedetomidine is highly protein bound (>90%) and undergoes extensive hepatic metabolism. The resulting methyl and glucuronide conjugates are excreted by the kidneys. Dexmedetomidine has weak inhibiting

effects on cytochrome P4S0 enzyme systems that might manifest as increased plasma concentrations of opioids as administered during anesthesia.[72]

Dose: 1µg/kg over 10 minutes as bolus and 0.2-0.7µg/kg/hour

Availability:

Available as 1ml and 2ml ampoules containing 50µg in each ml

Uses:

- Anxiolysis
- Premedication in children
- ICU and Procedural sedation
- Adjuvant in caudal anaesthesia

Side effects

- Hypotension
- Bradycardia
- Hypertension(Rare)

PERIOPERATIVE SHIVERING AND ITS CONTROL

Perioperative shivering can be broadly described under neuraxial anaesthesia and post anaesthetic shivering usually following general anaesthesia. Shivering is an involuntary, oscillatory muscular activity that augments metabolic heat production. It may increase the metabolic heat production up to 600% above

basal level. Shivering is elicited when the preoptic region of the hypothalamus is cooled.

Efferent signals mediating shivering descend in the medial forebrain bundle. Thermally-induced changes in neuronal activity in the mesencephalic reticular formation and the dorsolateral pontine and medullary reticular formation exert descending influences on the spinal cord that increase muscle tone[1].

Spinal alpha motor neurons and their axons are the final common path for both coordinated movement and shivering. A typical cold tremor has a specific rhythm in the form of grouped discharges in the electromyography .The fundamental tremor frequency on the electromyogram in humans is typically near 200 Hz.

The basal frequency is modulated by a slow, 4-8 cycles/ min, waxing and waning pattern. During continued cold stimulation of the skin or the spinal cord, motor neurons are recruited in sequence of increasing size, starting with the small gamma motor neurons that are followed by the small tonic alpha motor neurons, and finally, the larger phasic alpha motor neurons[1].

ABNORMAL TREMOR PATTERNS:

There are three patterns of muscular activity observed in hypothermic volunteers during recovery. The first was a tonic stiffening and appeared largely as direct non-temperature dependent effect of anaesthesia. A second pattern was overt synchronous tonic waxing and waning pattern. This was the most common pattern and resembled that produced by cold induced true thermoregulatory shivering. The third pattern was spontaneous electromyographic clonus[1].

Shivering can double or even triple oxygen consumption and carbon dioxide production. These large increases in metabolic requirement may

predispose patients with existing intrapulmonary shunts, fixed cardiac output, or limited respiratory reserve to a severe compromised state.[59]

POST ANAESTHESIA SHIVERING

Shivering is remarkably uncomfortable for the patient and some even find the accompanying cold sensation worse than the surgical pain. Stretching of the incision site may aggravate the post operative pain. It also raises the intraocular pressure, intracranial pressure and monitoring techniques.[59] Shivering is very evident in the recovery room, the most likely explanation for this is anaesthesia induced inhibition of thermoregulation which dissipates abruptly, thereby increasing the shivering threshold towards normal.[59] Core body and skin hypothermia remains the most common cause of shivering post operative shivering[1].

Chapter 5

Methodology

METHODOLOGY

The present study was conducted in the Department of Anaesthesiology, KLES Hospital and MRC, Belgaum during the period of January 2013 to December 2013

Study Design

One year double blinded randomized controlled trial

Source of Data:

Patients undergoing infraumbilical surgeries under spinal anaesthesia at K.L.E.S. Hospital and M.R.C., Belgaum

Sample Size:

A total sample size of 60 cases, 30 in Group A and the other 30 in Group B

Sample Size calculation:

The sample size was calculated by considering incidence of shivering as 15% with Inj.Dexmedetomidine 1µg/kg over 10 minutes and with that of normal saline as 55%.[13] With type I error rate $\alpha = 0.05$ and type II error rate $\beta = 0.02$ with a power of 80% and using the formula-

$$n=\frac{2\,(Z\alpha+Z\beta)^2\,pq}{(p_0-p_1)^2}$$

Thus the sample size obtained was 60, which was divided into two groups of 30 each.

Inclusion Criteria:

- ASA physical status I and II.
- Age between 18 to 60 years.
- Patient undergoing Infra umbilical surgery under spinal anaesthesia with a minimum duration of 45 minutes to 1 hour

Exclusion Criteria:

- Patients not willing to give consent
- Allergic to the study drugs-bupivacaine and dexmedetomidine
- A Pre-Operative baseline temperature of more than 37.5 degree Celsius
- Patients on long standing opioids
- Patients suffering from thyroid disorders
- Patient undergoing surgeries like TURP, where irrigation fluids are used
- Patients who are known case of liver disease

Duration of Study:

January 2013 to December 2013

Methodology:

After obtaining the approval of the Ethical committee and written informed consent, a total of 60 patients confirming to the inclusion and exclusion criteria were included in the study.

Patients were randomly divided into two groups, Group A who would be administered dexmedetomidine and Group B who would be administered 0.9 % normal saline, by using computer generated table. An investigator who was not otherwise involved in the study prepared syringes containing saline or dexmedetomidine; thus, the study was double-blinded The temperature of the operating room was maintained at a constant temperature between 22 to 24 degree Celsius (measured by a wall thermometer).

Before performing spinal anaesthesia, each patient received 10 ml/kg of lactated Ringer's solution half an hour before spinal anaesthesia. Patient was shifted to Operation theatre and standard monitors for measurement of heart rate, SPO2, blood pressure and ECG changes were connected.

After taking a baseline reading, following the guidelines for asepsis, subarachnoid anaesthesia was instituted at the L3-4 interspace.

3 ml of hyperbaric bupivacaine was injected using a 23G Quincke spinal needle, with bevel facing upwards.

Group A was given an i.v. infusion of dexmedetomidine 1 µg/kg, administered by diluting 200 µg (2ml) of the drug diluted upto 50ml, resulting in a solution strength of 4 µg/ml. It was administered using a syringe pump over a

20-min period. Group B received an equal volume of saline. After 10 minutes of administration of spinal anaesthesia, level of sensory blockade was assessed using spirit swab, whereas motor blockade was assessed by Modified Bromage scale as follows

0 = No Motor Block

1 = Can flex knee, move foot, but cannot raise leg

2 = Can move foot only

3 = Cannot move foot or knee

The patient's temperature was recorded every 15 minutes and continued up to 3 hours after giving the subarachnoid blockade, using a tympanic membrane temperature probe.

Intravenous fluids were administrated at room temperature and given without inline warming. Supplemental oxygen (5l/min) was delivered via a facemask during the operation.

All patients were covered with one layer of surgical drapes over the chest, thighs, and calves during the operation and then one cotton blanket over the entire body. No other warming device was used. A core temperature below 36˚C was considered hypothermia.

The presence of shivering was assessed by a blinded observer after the completion of subarachnoid drug injection.

Shivering was graded on a scale:

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,

4 = shivering involving the whole body.

The incidence and severity of shivering was recorded at 15-min intervals during the operation and in the recovery room. If score was three or greater Inj. Tramadol 1mg/kg IV was administered. Side effects, such as headache, allergy, hypotension, bradycardia, sedation, nausea and vomiting, if any were recorded.

If the patient's heart rate fell below 60 bpm, 0.6 mg atropine was administered i.v.

Hypotension was defined as a decrease in the mean arterial pressure (MAP) of more than 20 % from baseline. Hypotension was treated with 6 mg mephenteramine via i.v. bolus and then with further i.v. infusion of lactated Ringer's solution as required.

If patients developed nausea and vomiting, ondansetron 0.08mg/kg was administered through the intravenous route.

At intervals of 15 minutes, the attending anaesthesiologist assessed the degree of sedation on 5-point scale:

1 = fully awake and oriented,

2 = drowsy,

3 = eyes closed but open on command,

4 = eyes closed but open to mild physical stimulation,

5= eyes closed and unresponsive to mild physical stimulation.

STATISTICAL ANALYSIS

All statistical data were analyzed using SPSS 11.0. Demographic and Parametric data was analyzed by student unpaired-t test. Non- parametric data was analyzed by using Mann Whitney Test. P value of less than 0.05 was considered significant

Chapter 6

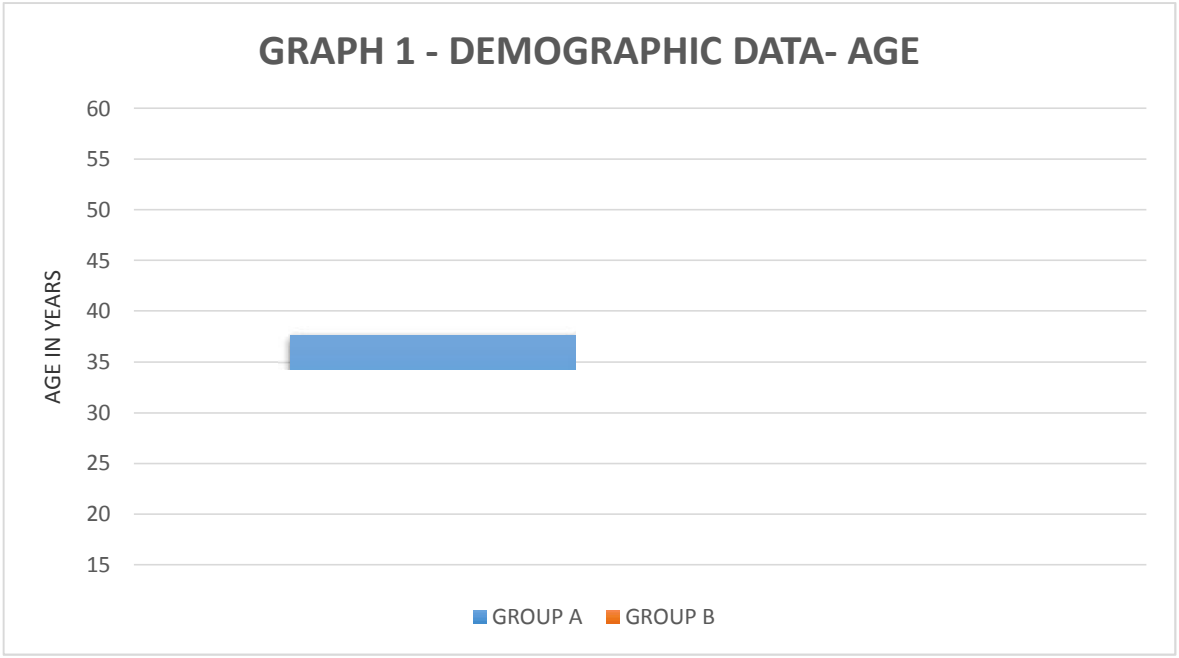
RESULTS

The present study was conducted in Department of Anaesthesiology, K.L.E.S. Hospital and M.R.C., Belgaum during the period of January 2013 to December 2013. 60 patients posted for infraumbilical surgery under spinal anaesthesia were divided into two groups, Group A- Dexmedetomidine (n=30) and Group B - 0.9% saline (n=30). At the onset of shivering, Grade III and above Inj.Tramadol 1mg/kg was administered intravenously and effects observed and recorded. Side effects if any, of the study drug were also noted.

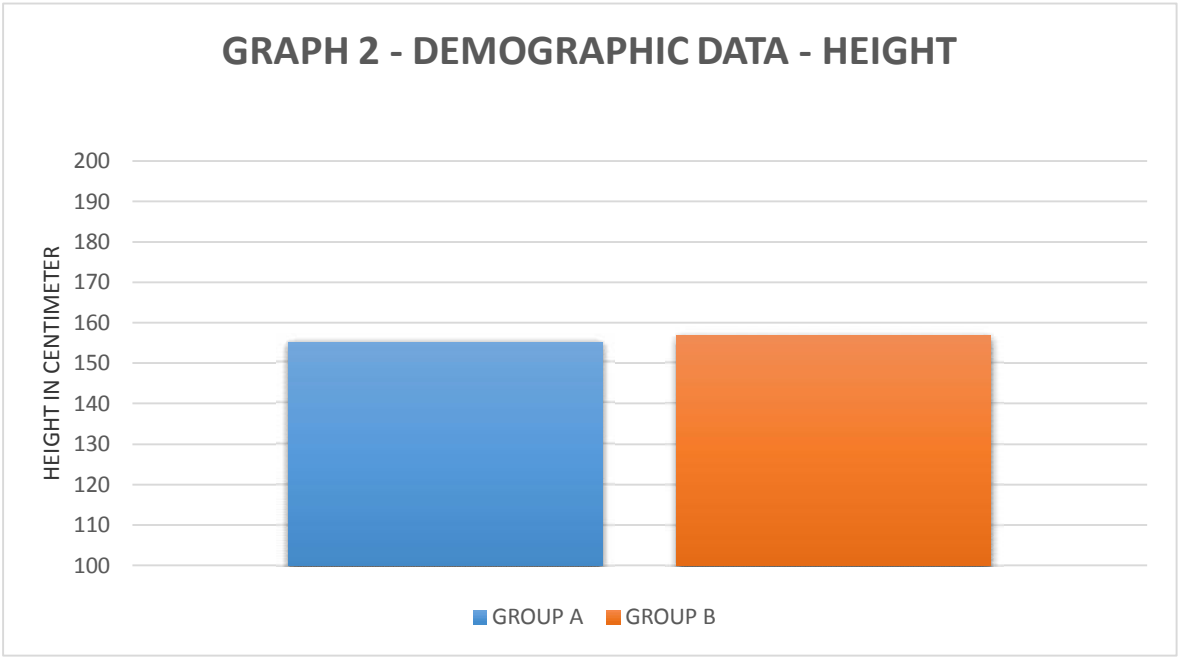
Table 1 – Demographic Data.

PARAMETER	**Group A (Mean ± S.D.)**	**Group B (Mean ± S.D.)**	**P Value**
Age(in years)	37.7 ± 8.21	40.6 ± 1.28	0.0609
Height(in cm)	155.2 ± 20.53	156.9 ± 8.88	0.6787
Weight(in kg)	65.11 ± 14.67	60.13 ±9 .37	0.1226
Duration of Surgery (in minutes)	88.93 ± 34.16	82.73 ± 46.84	0.5604
Sex(M/F)	17/13	16/14	
ASA status(1/2)	25/5	24/6	

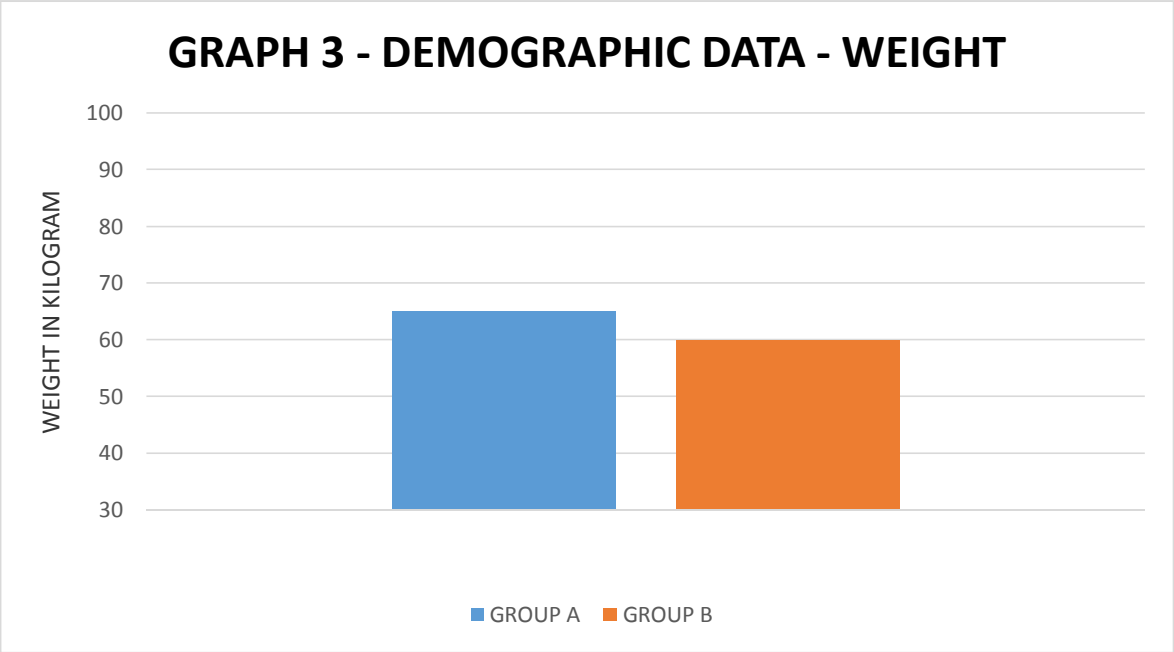
Demographic data was comparable in both the groups.



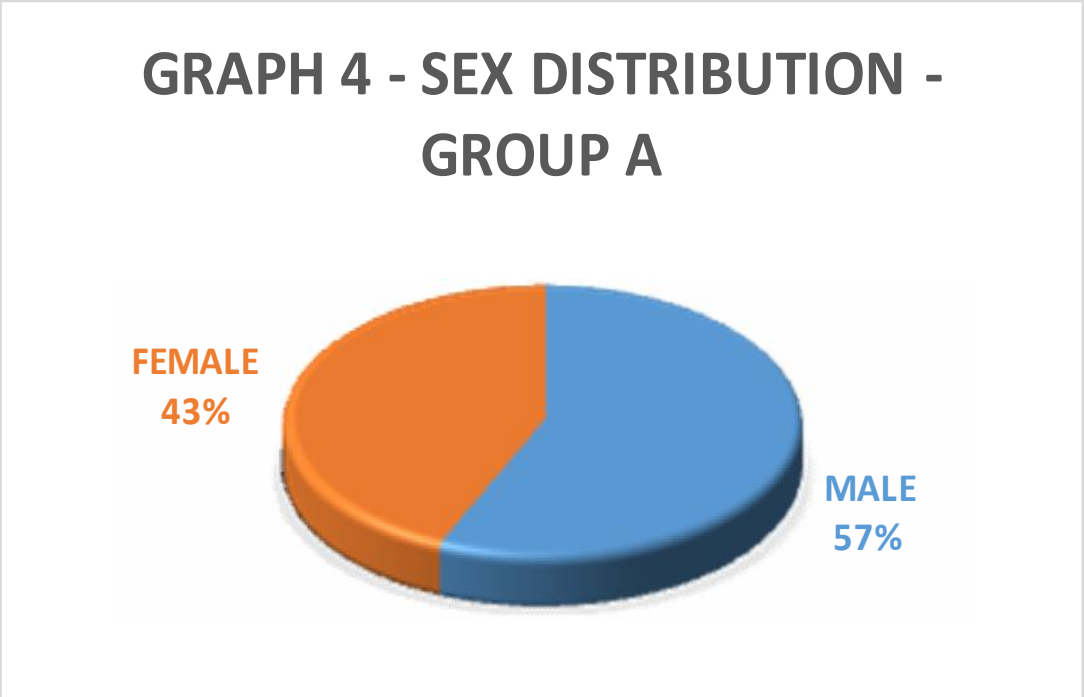
Average age in the Group A (Dexmedetomidine) was 37 years, in Group B (Placebo) was 40 years



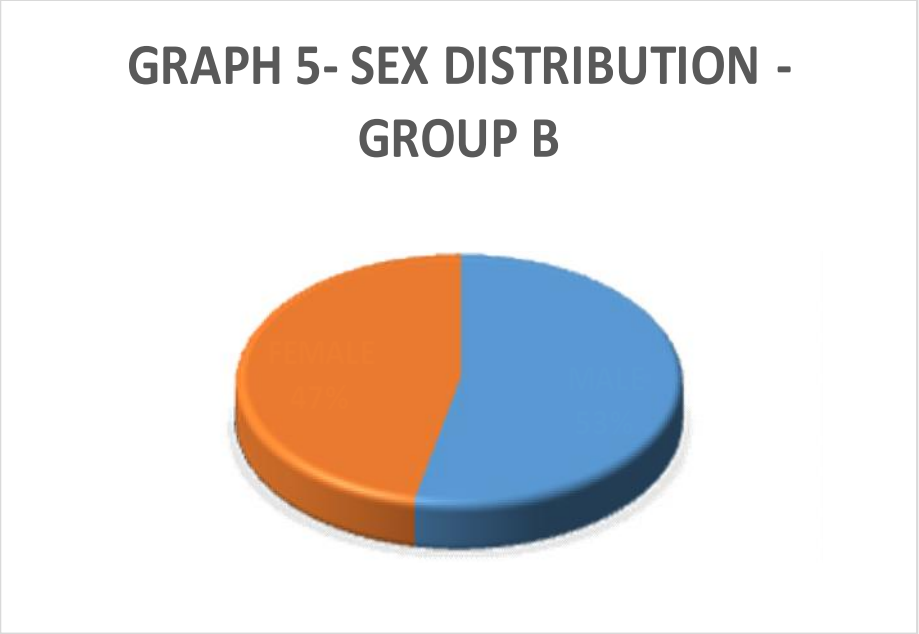
Average Height in Group A (Dexmedetomidine) was 155 cm, in Group B (Placebo) was 156 cm



Average weight in the Group A (Dexmedetomidine) was 65 kg, in Group B (Placebo) was 60 kg



Of the total 30 patients in Dexmedetomidine group 17 (57%) were males and 13(43%) were females.



Of the total 30 patients in Placebo group 16 (53%) were males and 14(47%) were females.

When compared the difference between the two groups was not found to be statistically significant.

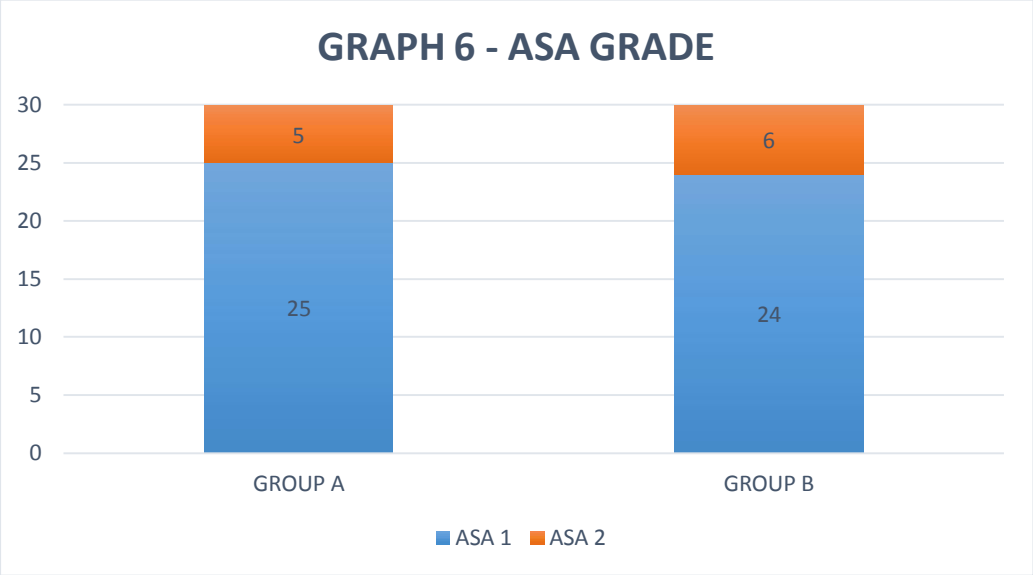
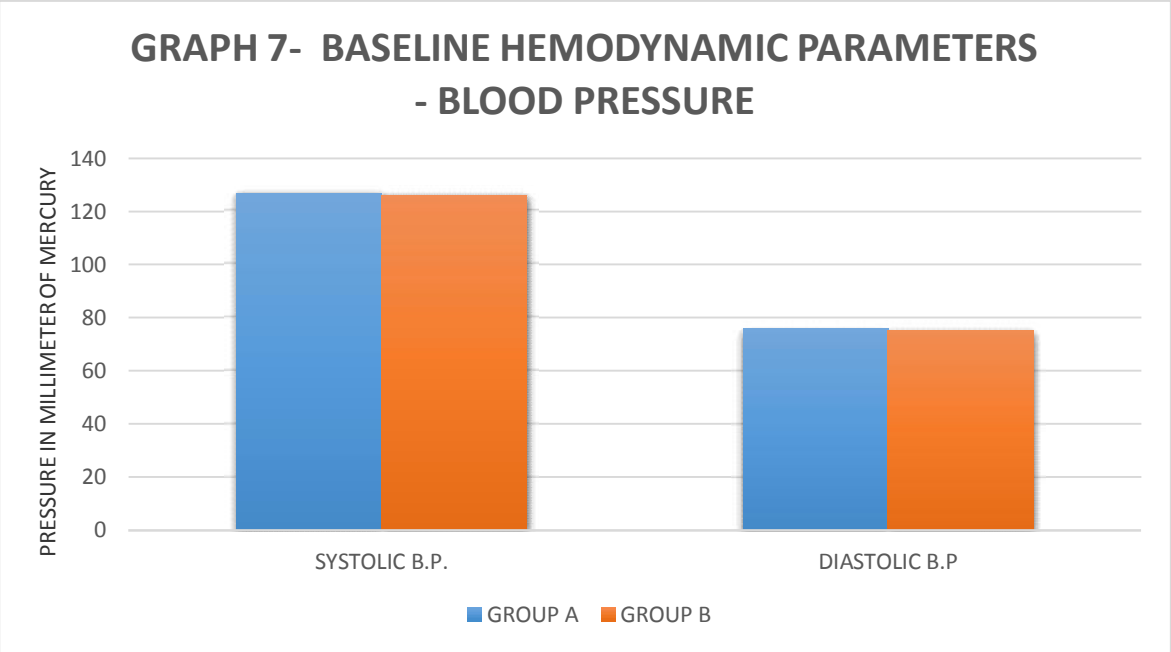


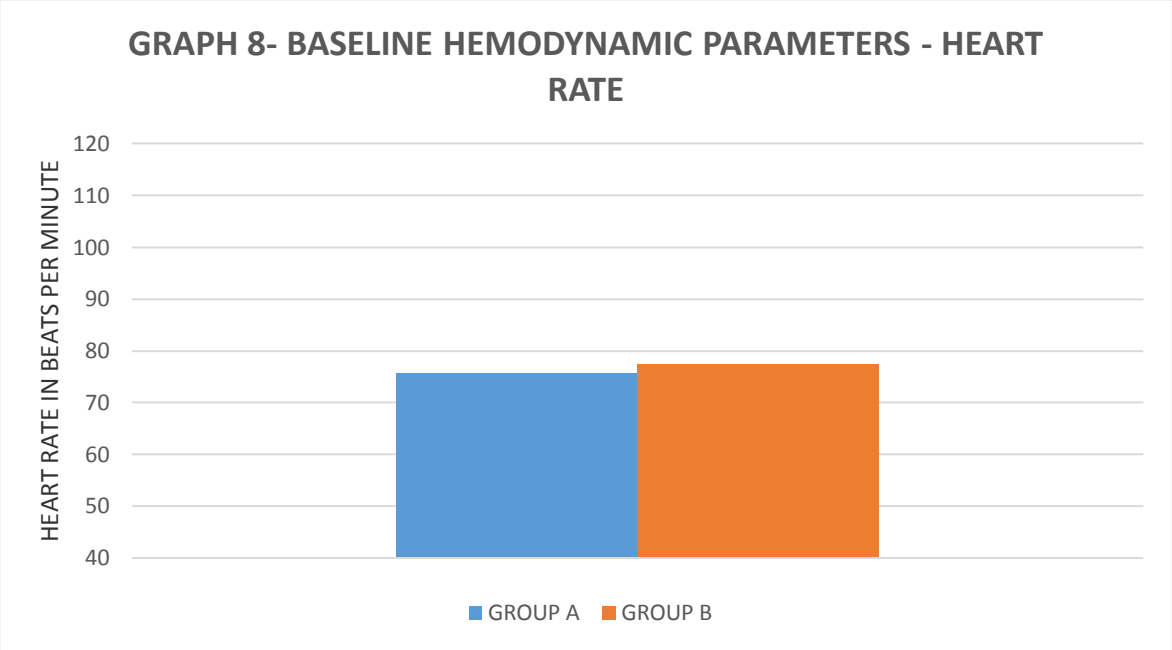
Table 2- Baseline Hemodynamic Parameters

PARAMETER	Group A (Mean ± S.D.)	Group B (Mean ± S.D.)	P Value
Systolic Blood Pressure (in mm of Hg)	126.86 ± 8.43	126.06 ± 10.9	0.7516
Diastolic blood pressure (in mm of Hg)	75.93 ± 7.22	75 ± 7.51	0.6267
Heart Rate(Beats per minute)	75.63 ± 9.21	77.43 ± 9.76	0.4655
Pre Operative Temperature(in Celsius)	36.66 ± 0.07	36.64 ± 0.06	0.2396



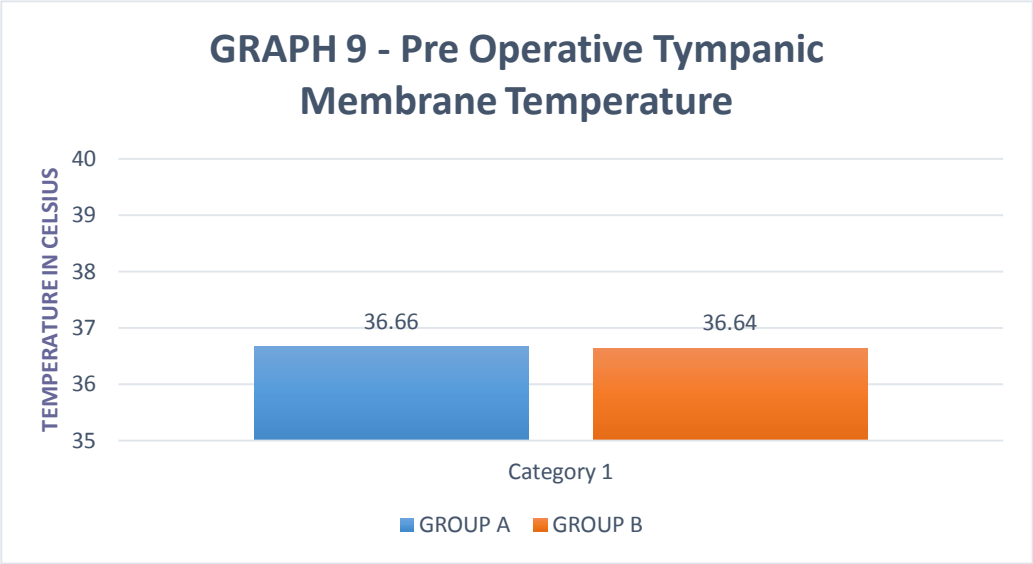
Systolic Blood Pressure in Group A (Dexmedetomidine) was 126.86 mm of Hg, in Group B (Placebo) was 126.06 mm of Hg.

Diastolic Blood Pressure in Group A (Dexmedetomidine) was 75.63 mm of Hg, in Group B (placebo) was 77.43 mm of Hg.



Heart Rate in Group A (Dexmedetomidine) was 75 beats/minute, in Group B (placebo) it was 77 beats/minute

Baseline hemodynamic and temperature parameters were comparable in both the groups.



Pre operative temperature in the Group A (Dexmedetomidine) was 36.66 degree Celsius, in Group B (Placebo) it was 36.64 degree Celsius.

TABLE 3 – Average level of sensory and motor blockade in the two groups

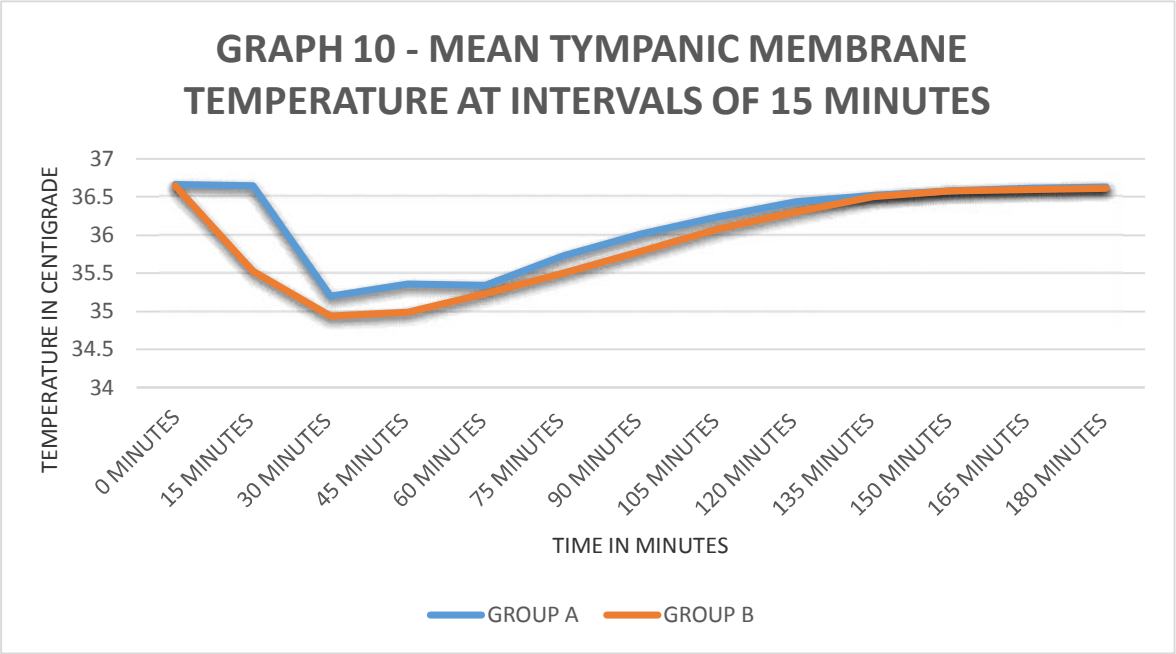
Group	Sensory Blockade (Thoracic dermatome)	Motor blockade (Modified Bromage Scale)
Group A	5.5	3
Group B	5.5	3

The average level of sensory blockade in Group A(Dexmedetomidine) was thoracic 5^{th} - 6^{th} (5.5) dermatome and that in Group B(Placebo) was thoracic5th - 6^{th} (5.5) dermatome. The motor blockade as per Modified Bromage scale was 3 in both the groups.

TABLE 4- MEAN TYMPANIC MEMBRANE TEMPERATURE AT INTERVALS OF 15 MINUTES

	TIME INTERVAL					
Group	Pre op 0 minutes	15 minutes	30 minutes	45 minutes	60 minutes	75 minutes
Group A	36.66	36.64	35.20	35.36	35.34	35.73
Group B	36.64	35.33	34.94	34.99	35.23	35.50

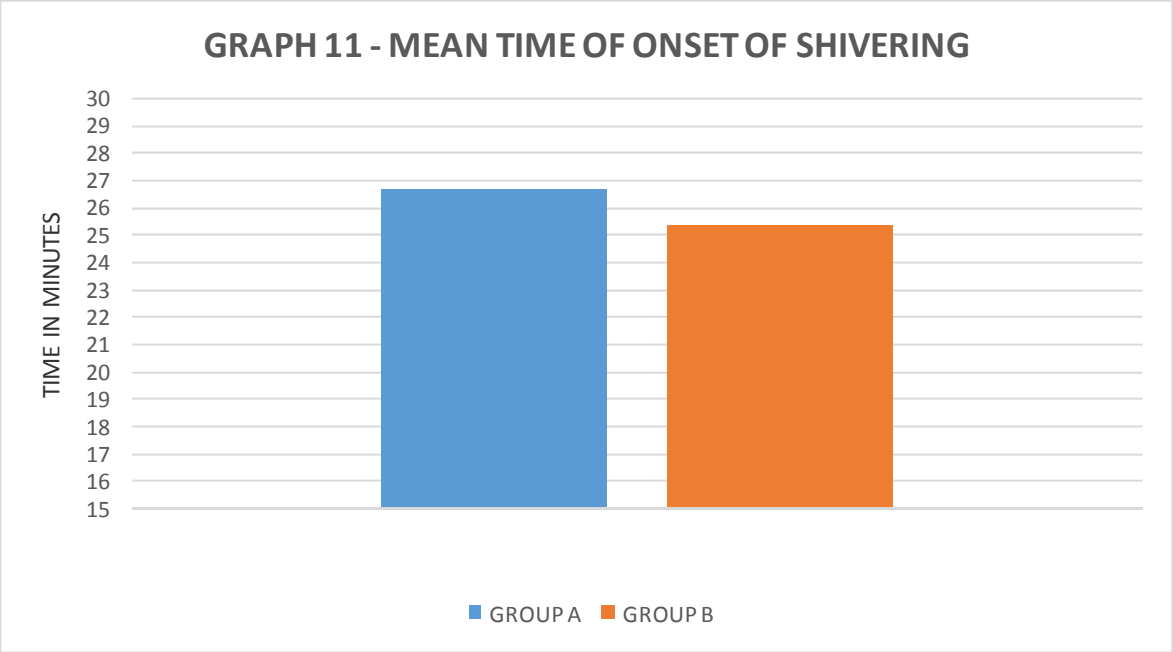
	TIME INTERVAL						
Group	90 minutes	105 minutes	120 minutes	135 minutes	150 minutes	165 minutes	180 minutes
Group A	36.01	36.24	36.43	36.52	36.58	36.61	36.63
Group B	35.79	36.08	36.30	36.5	36.58	36.59	36.61



The minimum Temperature recorded in Group A (Dexmedetomidine) was at 30 minutes (35.20 degree Celsius) after the start of surgery, whereas in Group B (Placebo) it was at 30 minutes (34.94 degree Celsius) after the start of surgery.

Table 5 - MEAN TIME OF ONSET OF SHIVERING IN THE TWO GROUPS

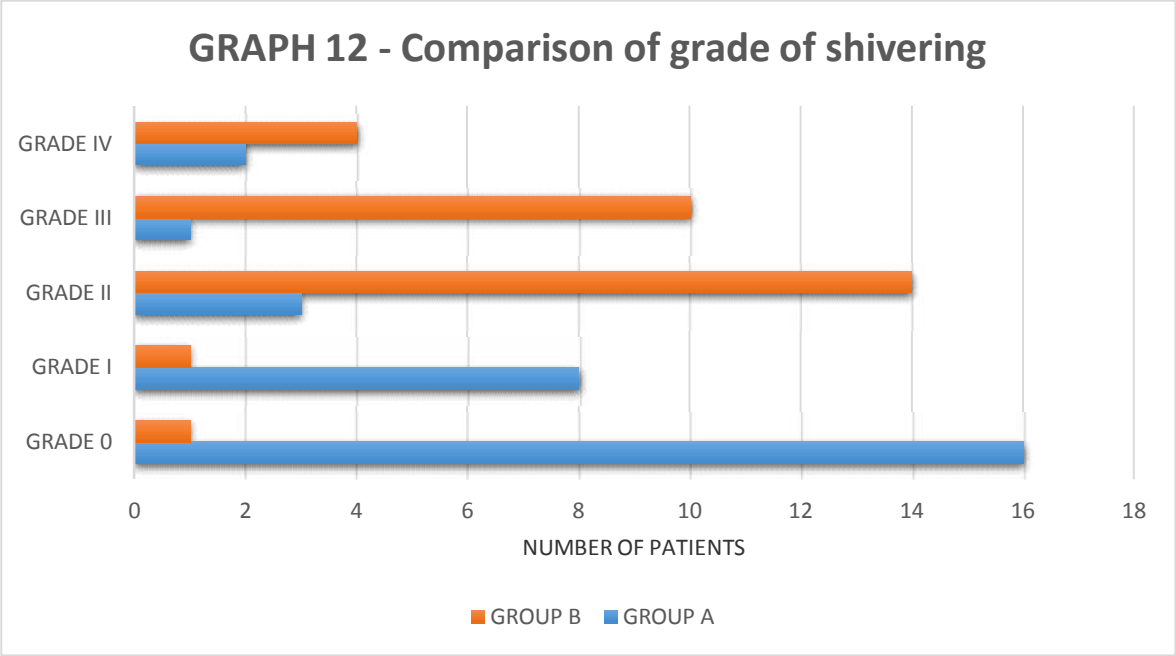
GROUP	ONSET OF SHIVERING (IN MINUTES)
GROUP A	26.66
GROUP B	25.375



Mean onset time of shivering in Group A (Dexmedetomidine) was 26.66 minutes whereas in Group B (placebo) it was 25.37 minutes

Table 6 - Comparison of grade of shivering in the two groups

Grade	**Group A**	**Group B**
Grade 0	16	1
Grade I	8	1
Grade II	3	14
Grade III	1	10
Grade IV	2	4

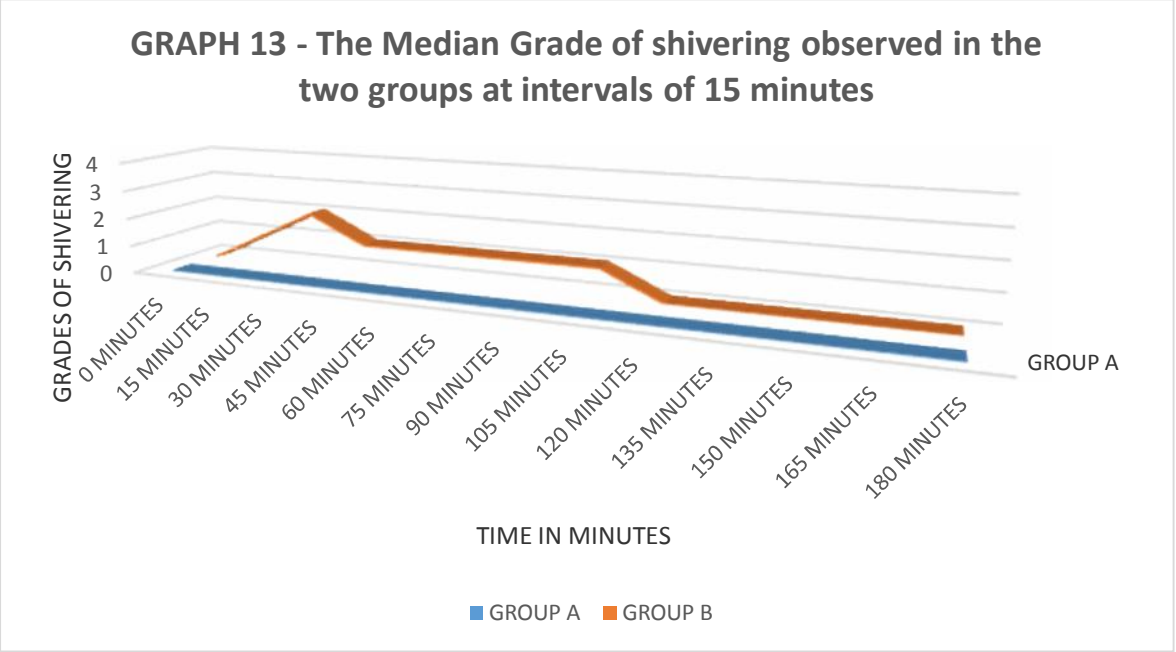


Majority of the patients in Group A (Dexmedetomidine) 16 had a shivering grade of 0 whereas in the Group B (Placebo) (14) majority had a shivering grade of II

Table 7 – Median Grade of shivering in the two groups at intervals of 15 minutes

TIME (MINUTES)	Group A (n=30)	Group B (n=30)	p Value
0	0	0	
15	0	1	0.0051
30	0	2	0.0001
45	0	1	0.0001
75	0	1	0.0001
60	0	1	0.0001
90	0	1	0.0001
105	0	1	0.0008
120	0	0	0.0009
135	0	0	0.0068
150	0	0	0.0979
165	0	0	0.1555
180	0	0	0.1212

Median grades of shivering at intervals of 15 minutes are shown in the table above.



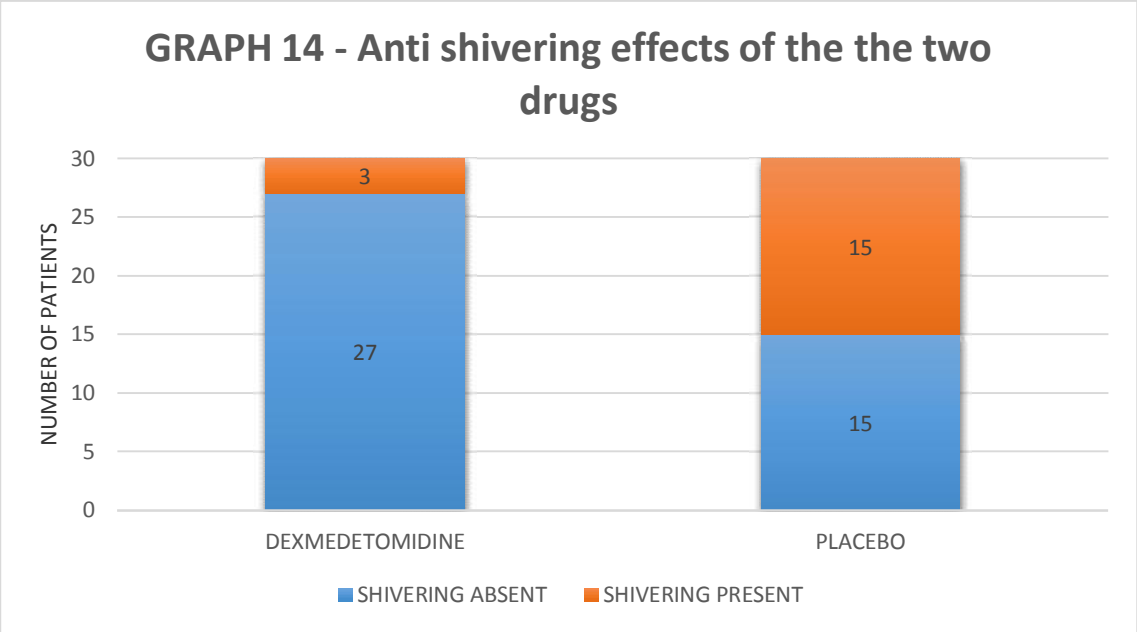
The Median grade of shivering in Group A (Dexmedetomidine) was 0, whereas in Group B (Placebo) median grade of 2 was observed at 30 minutes from the start of procedure.

Results from our data showed that there was significant difference in the antishivering effect upto 135 minutes, after which it was insignificant

TABLE 8 – Anti shivering effects of the the two drugs

TABLE 6

DRUG	Anti Shivering Effect
Dexmedetomidine	27/30 (90 %)
Placebo	15/30 (50 %)

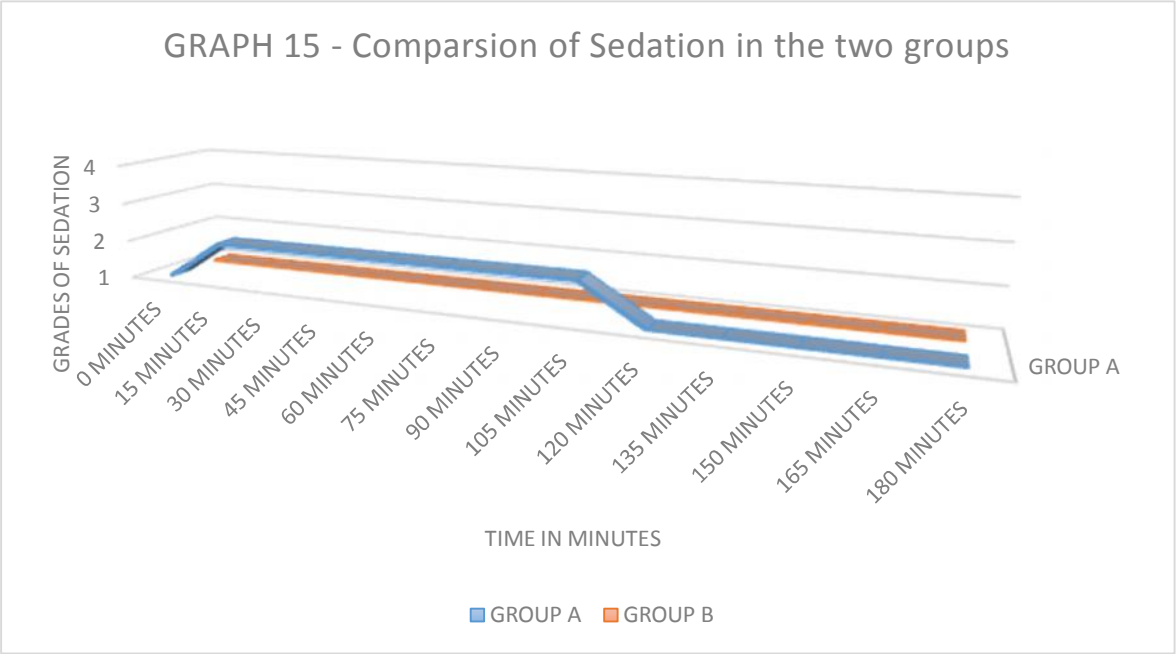


In the Group A (Dexmedetomidine) the number of patients who did not experience shivering throughout the procedure were 27 out of 30 (90 %)

In the Group B (Placebo) the number of patients who did not experience shivering throughout the procedure were 15 out of 30 (50%)

Table 9 – Comparsion of Sedation in the two groups

TIME (MINUTES)	Group A (n=30)	Group B (n=30)	p Value
0	1	1	>0.05
15	2	1	0.0001
30	2	1	0.0001
45	2	1	0.0001
60	2	1	0.0001
75	2	1	0.0001
90	2	1	0.0009
105	2	1	0.0216
120	1	1	0.6080
135	1	1	0.7232
150	1	1	0.1555
165	1	1	>0.05
180	1	1	>0.05

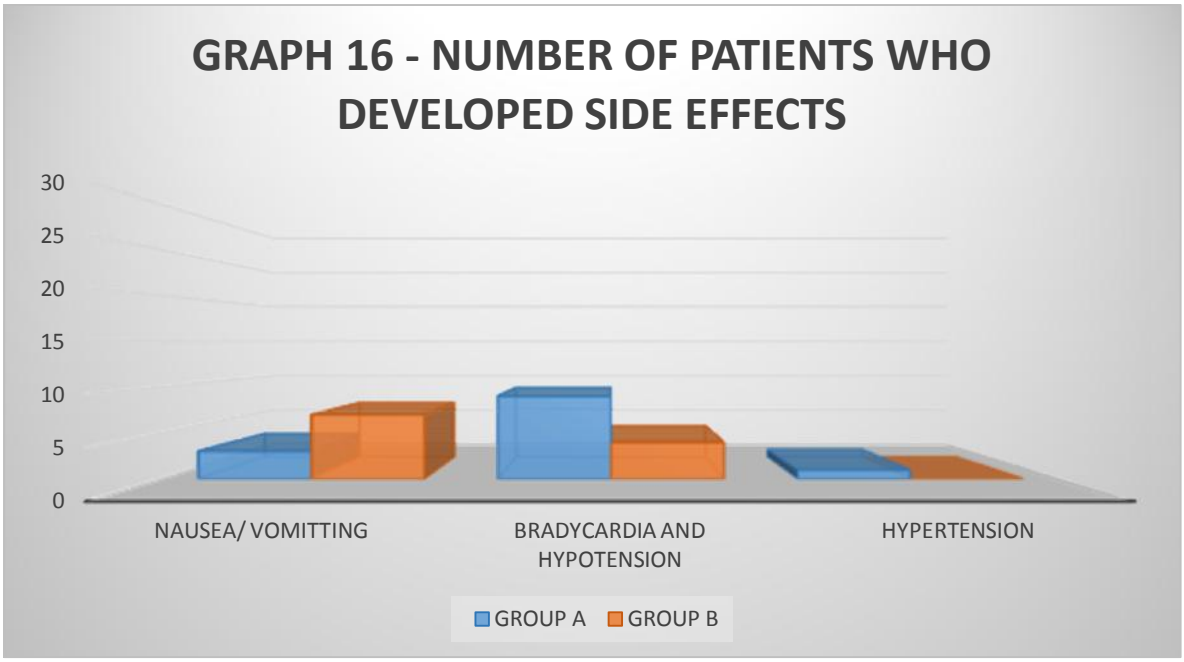


The grades of sedation in Group A (Dexmedetomidine) were comparatively higher (grade 2) upto 105 minutes whereas in the Group B (Placebo) it was grade 1 throughout the procedure

SIDE EFFECTS

TABLE 10 – SIDE EFFECTS

SIDE EFFECTS	GROUP A DEXMEDETOMIDINE	GROUP B PLACEBO
NAUSEA / VOMITTING	3/30	7 / 30
BRADYCARDIA AND HYPOTENSION	9/30	4/30
HYPERTENSION	1/30	0/30



Incidence of nausea / vomiting in Group A (Dexmedetomidine) was 10 % (3/30), whereas in Group B (Placebo) it was 23 % (7/30)

Incidence of Bradycardia and hypotension in Group A (Dexmedetomidine) was 30 % (9/30), whereas in Group B (Placebo) it was 13.3 % (4/30)

In Group A (Dexmedetomidine) hypertension occurred in 3.3% (1/30)

Chapter 7

Discussion

DISCUSSION

Shivering is quintessential in our practice. It occurs during both general and spinal anaesthesia. The exact mechanism of shivering is not known but the probable mechanisms involved in shivering are loss of heat, systemically released pyrogens, reduced sympathetic tone, increased cutaneous blood flow leading to increased heat loss from skin. Shivering causes increase in oxygen demand, CO_2 production and lactic acidosis. There is also evident increase in intracranial and intraocular pressures. During Neuraxial blockade there is redistribution of heat from the core to the periphery. There occurs to be a loss a feedback of temperature changes to the central nervous system, from the lower limbs because of the blockade through the afferents carrying these signals.

Various risk factors associated with shivering have been mentioned. To name a few they are:

- young age
- male sex
- longer duration of anesthesia
- Type of anaesthesia

A patient may become hypothermic because of the above mentioned factors in addition to the reduced temperatures in the operating room and the temperature of the intravenous fluids.[1,59] In our study we have eliminated the bias by having population with similar characteristics in both groups in relation to age, sex, duration of surgery and the type of anaesthesia which was spinal anaesthesia. The

average level of sensory blockade in Group A (Dexmedetomidine) was thoracic 5^{th} to 6^{th} dermatome and that in Group B(Placebo) was thoracic 5^{th} to 6^{th} dermatome. The motor blockade as per Modified Bromage scale was 3 in both the groups.

As patients in both the groups were found to have similar levels of sensory and motor blockade, therefore the bias related to these factors was eliminated.

Various pharmacological and non pharmacological methods have been tried to prevent as well as treat shivering

The non-pharmacological methods used are:

- Covering the patient with sterile cotton bed sheets
- Hot air blowers
- Regulating the operating room temperature

Pharmacological agents used in shivering are:

- Ketamine
- Pethidine
- Tramadol
- Dexmedetomidine
- Granisetron
- Magnesium sulphate

It is known that core body temperature undergoes rapid changes in the perioperative period. The temperature measurement shows variations based on the sites of measurement. Of the available sites, the tympanic membrane monitoring is considered to be safer and comfortable in comparison to esophageal and rectal site temperature monitoring which make an awake patient uncomfortable. Tympanic membrane temperature monitoring is also more specific to changes in the core body temperature and hence we monitored the temperature changes in the intra and the post operative periods using a tympanic membrane temperature probe[1].

In the present study we recorded the baseline temperature of the patient during the preoperative period. This was followed by measurements of temperature at intervals of 15 minutes, up to 180 minutes after administration of spinal anaesthesia.

As the onset of shivering occurs within 5 to 45 minutes of blockade[11], we started the infusion of drugs in both the groups immediately after administration of the sub arachnoid blockade

In our study, Dexmedetomidine 1 µg/kg over 20 minutes after administration of spinal anaesthesia was found to have a significant role in reduction of occurrence of shivering in comparison to 0.9 % Normal Saline. Dexmedetomidine acts on the α2A receptors in brain and spinal cord leading to an increased threshold for shivering.

The number of patients who did not experience shivering in the Dexmedetomidine group was 27 out of 30 (90%). In the 0.9 % Normal Saline Group was 15 out of 30 (50 %).

We found that onset of shivering in both the groups was the same, which was 30 minutes after administration of spinal anaesthesia.

Median grade of shivering at intervals of 15 minutes, following administration of spinal anaesthesia was significantly lower in the Dexmedetomidine group in which it was found to be Grade 0 throughout the monitoring period of 180 minutes, while for 0.9 % normal saline it was grade 2 at 30 minutes, after which it reduced to grade 1 and zero after the administration of Inj. Tramadol

The antishivering effect in the dexmedetomidine group was thus present throughout the procedure compared to 0.9% normal saline where peak shivering was noted at 30 minutes

Results of the data observed in our study showed the efficacy of Dexmedetomidine in prevention of shivering, in comparison with 0.9% normal saline, with the P value being <0.05 . The difference became insignificant between the two groups after an interval of 150 minutes.

Efficacy of Dexmedetomidine and meperdine was studied by Bicer and his colleagues. They compared dexmedetomidine 1µg/kg with meperidine 0.5mg/kg and 0.9% saline as placebo in 120 patients for their action on

prevention of post anaesthetic shivering in elective abdominal or orthopaedic surgeries under General anaesthesia. Results showed that both Dexmedetomidine 1µg/kg and 0.5mg/kg pethidine were useful in prevention of shivering and there was no statistically significant difference between them.[13]

DeRike X et al mentioned in their study that during wound closure for procedures under General Anaesthesia, dexmedetomidine successfully reduced the shivering threshold and vasoconstriction threshold in healthy volunteers. Dexmedetomidine (1 µg/kg) given at the time of wound closure significantly reduced postanesthesia shivering when compared to saline [15% vs. 55%, respectively] and was comparable to meperidine 0.5 mg/kg (10%). Compared to the control group (saline), dexmedetomidine and meperidine significantly lowered the shivering threshold by 0.7 degree Celsius and 1.2 degree Celsius, respectively. They also concluded that this agent deserves further study for its utility in the clinical setting of moderate hypothermia.[14]

Our studies had similar results, but unlike these studies, our study was done in patients undergoing spinal anaesthesia. Here it was found that, Dexmedetomidine 1 µg/kg over 20 minutes had a significant anti shivering effect. Mepridine is not preferred because of its adverse effects like nausea, vomiting, respiratory depression and itching. Thus, we did not use it in our study.

Elvan and his colleagues studied dexmedetomidine for its effects on shivering in women undergoing elective hysterectomies. 90 ASA I and II were included in the study and were divided into two groups of dexmedetomidine and placebo, of 45 each. Dexmedetomidine was administered as a loading dose of

1µg/kg over 10 minutes, followed by a maintenance infusion of 0.4µg/kg/hour. They found that only 7 out of 45 patients in the dexmedetomidine group experienced shivering, Ramsay sedation was also found to be higher in the dexmedtomine group over the first hour.[15]

Our studies had similar results with dexmedetomidine having significant anti shivering effect and higher grade of sedation when compared to the placebo group over a similar period of time.

Ghazi A examined the efficacy of alpha 2 agonist Dexmedetomidine in prevention of shivering in 70 patients undergoing surgeries under general anaesthesia. Dexmedetomidine 1µg/kg or normal saline were given over 10 minutes, 20 minutes before the end of the procedure. He found that shivering was of grade 0 in 88.5 % of patients in the dexmedetomidine group and 54 % of patients in the saline group. Hence he concluded that dexmedetomidine 1µg/kg was safe and effective in prevention of post operative shivering[10].

Our study under spinal anaesthesia found similar results, but we started the infusion of dexmedetomidine 1µg/kg over 20 minutes immediately after administration of spinal anaesthesia

Bajwa et al investigated the reduction in incidence of shivering with perioperative dexmedetomidine in 80 patients undergoing general anesthesia for laparoscopic surgeries. 40 patients received Dexmedetomidine 1µg/kg in 2 ml saline over 10 minutes, 30 minutes before the end of the surgery. The rest 40

patients received saline over 10 minutes. There was significant difference in the grades of shivering ($P < 0.05$) between the two groups. And they concluded that dexmedetomidine seemed to have antishivering effect in a dose of 1µg/kg and patients also had a side effect of dry mouth and sedation.[9]

We found the similar effect of dexmedetomidine on shivering in a dose of 1µg/kg and the incidence of shivering was 10% and 50% in Dexmedetomidine and placebo group respectively. We also found that patients were more comfortable with administration of dexmedetomidine because of its anxiolytic, analgesic and sedative actions.

Kim et al conducted a study on evaluation of optimal dose of dexmedetomidine and 0.9 % normal saline in the prevention of post anaesthesia shivering in 130 patients. They used 3 doses of dexmedetomidine which were 0.5, 0.75, 1 µg/kg in 3 different groups. They concluded that groups of 0.75 and 1 µg/kg had lesser incidence of shivering and lesser requirement of rescue drug.

In our study we used a dose of 1µg/kg of dexmedetomidine over 20 minutes and it prevented the occurrence of shivering significantly. In addition to the antishivering effect, it was also found that requirement of rescue drug was also very less when compared to the 0.9% normal saline group.[16]

Usta and his colleagues conducted a study to evaluate the effect of dexmedetomidine on shivering during spinal anesthesia. Of the 60 patients selected, 30 patients were administered 0.9% normal saline and the other 30 patients were given Dexmedetomidine at 1 µg/kg over 10 minutes, followed by 0.4 µg/kg/hour until skin incision. Their results showed that the occurrence of

shivering in dexmedetomidine group was only 10 %, compared to the 0.9% normal saline group, where it was 56.4%.[11]

Our study was differing from their study, as we used dexmedetomidine only in a dose of 1 µg/kg over 20 minutes. We found similar results where the shivering in the group dexmedetomidine was 10% versus the 0.9% normal saline group where it was found to be 50%.

Bozgeyik et al compared the effects of preemptive tramadol and dexmedetomidine for their ability in prevention of shivering during arthroscopy. Of the total 90 patients, 30 received 100 mg tramadol in 100 ml saline in group T- (n = 30) and 0.5 µg/kg dexmedetomidine in 100 ml saline in group D- (n = 30) and 100 ml saline was administered in group P- (n = 30) in 10 min. They found that both the Dexmedetomidine and the tramadol were useful in prevention of shivering following spinal anaesthesia, and that dexmedetomidine group had better sedation scores.[17]

Our study was similar to this except that we used an infusion pump for delivering the drugs intravenously. Our results are similar to their study, where we found that dexmedetomidine was useful in prevention of shivering in significant number of cases, along with this, it also decreased the anxiety in them because of their sedative effect.

In a study by Mittal and her colleagues 50 patients were randomised in two groups of 25 patients each to receive either dexmedetomidine 0.5 µg/kg or tramadol 0.5 mg/kg as a slow intravenous bolus (diluted to a volume of 5 ml in a 5 ml syringe). They observed that time taken for cessation of shivering post

spinal anaesthesia was significantly less with dexmedetomidine when compared to tramadol. Nausea and vomiting was observed only in tramadol group (28% and; 20% respectively). Thus, they concluded that although both drugs are effective, the time taken for cessation of shivering is less with dexmedetomidine when compared to tramadol. Moreover, dexmedetomidine has negligible adverse effects, whereas tramadol is associated with significant nausea and vomiting.[18]

In our study we observed that 10 % (3 out of 30) of the patients in the Dexmedetomidine developed nausea/ vomiting. Whereas, the placebo group where 0.9% normal saline was used had a incidence of 23% (7 out of 30)in the intra operative period, all of these patients were administered inj. Ondansetron 0.08mg/kg IV.

Bradycardia and hypotension is a known complication with use of Dexmedetomidine, we found this effect to be evident in 30 % (9 out of 30) of the patients. On the other hand the placebo group it was found to be evident in 13% (4 out of 30) of the patients. Spinal anaesthesia itself causes bradycardia and hypotension, which may be additive to these adverse effects caused by dexmedetomidine, Hence it would be difficult to comment on the exact contribution of dexmedetomidine with respect to occurrence of bradycardia and hypotension. All patients suffering from bradycardia were given Inj. Atropine 0.6 mg IV

There was occurrence of elevated blood pressure which was 40 percent above the baseline MAP, in 1 patient in the Dexmedetomidine group. This occurred at 15 minutes after starting the infusion. However it was probably

anxiety induced and MAP returned to baseline value following reassurance and Inj. Midazolam 1mg IV.

Occurrence of shivering can be critical in compromised states where increased demand of oxygen can put the patient at jeopardy. Dexmedetomidine is now more easily available in most of the centers and amongst the many useful actions of this drug, anti shivering action is also one of them, which can be useful in our everyday practice.

Rather than waiting for the shivering to occur and then administer a drug which will have a lag period with respect to its onset of action, we can use Dexmedetomidine to avoid the occurrence of shivering and its related complications.

A limitation in our study was that we did not use a background maintenance infusion of dexmedetomidine to avoid the hemodynamic changes because of the above mentioned additive effects and further worsening of hemodynamics. However use of which would have further reduced the incidence of shivering in the intra operative and post operative periods.

In future lower doses and infusion rate of dexmedetomidine may be evaluated which may be associated with lesser incidence of side effects like hypotension and bradycardia.

Use of Dexmedetomidine in prevention of shivering in ICU setting may also be evaluated.

Chapter 8

Conclusion

CONCLUSION

In conclusion, Dexmedetomidine 1µg/kg over 20 minutes is a useful drug in prevention of shivering in patients undergoing infraumbilical surgeries under spinal anaesthesia. Dexmedetomidine was found to be effective to combat shivering and can be recommended in prevention of shivering, keeping in mind hypotension and bradycardia as its side effects.

Chapter 9

Summary

SUMMARY

The present study was conducted in the Department of Anaesthesiology, KLES Prabhakar Kore Hospital and MRC, Belgaum after obtaining an approval from institutional ethics committee and written informed consent.

The study included 60 ASA grade I and II patients, posted for infra umbilical surgeries under spinal anaesthesia. Thorough Pre Anaesthetic Evaluation was done and the basal core body temperature was recorded. Computer generated table was used for random allocation of patients into two groups- Group Dexmedetomidine and Group Placebo. Spinal Anaesthesia was administered with 3 ml of 0.5% heavy bupivacaine. Immediately after this, an infusion of the study drug was started by a blinded observer.

The core body temperature was recorded at intervals of 15 minutes for 180 minutes.

We observed that there was a fall in the temperature in both the groups and the least temperature recorded in Group Dexmedetomidine was at 30 minutes (35.20 degrees) and the least temperature in the placebo group was also noted at 30 minutes (34.94 degree Celsius)

Shivering was graded at intervals of 15 minutes and was recorded in both the groups.

The number of patients receiving Dexmedetomidine in whom shivering did not occur was 27 out of 30 (90 %) while in the placebo group 15 out of 30 (50 %) experienced shivering.

Results of the data observed from our study showed that Dexmedetomidine was effective in prevention of shivering throughout a period of 180 minutes, however the median grades of shivering were insignificant between the two groups after an interval of 150 minutes.

Bradycardia and hypotension is a known side effect of Dexmedetomidine. It was observed in 9 out of 30 patients who received Dexmedetomidine and also in 4 out of 30 patients in the placebo group. But of these how many occurred because of Dexmedetomidine cannot be commented upon, as spinal anaesthesia itself causes hypotension.

Nausea and or vomiting occurred in 3 out of 30 patients in the Dexmedetomidine group. Whereas it was observed in 7 out of 30 patients in the

placebo group. These were treated with ondansetron 0.08 mg/kg by intravenous route.

Thus based on the results we obtained, we conclude that Dexmedetomidine is an effective drug in prevention of shivering in patients undergoing infra umbilical surgeries under spinal anaesthesia.

Chapter 10

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Annexures

Annexure I

CONSENT FORM

Mr/Mrs/Miss. _____ we are requesting you to enrol yourself in study titled **"Efficacy of dexmedetomidine as an anti-shivering agent following spinal anaesthesia in adults" – A one year Randomized placebo controlled trial,** conducted by Dr. Avinash Kumar Jha, Post Graduate in M.D. Anaesthesiology under the guidance of Dr. Vandana Gogate M.D. Professor, Department of Anaesthesiology, J.N. Medical College, Belgaum under KLE university, Belgaum.

Respected Sir/Madam We request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

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.

The purpose of research is to know the effectiveness of dexmedetomidine in controlling intra operative shivering in patients undergoing spinal anaesthesia

Purpose of the study:

Dexmedetomidine is a new drug which has been shown to have a role in prevention of shivering in patients, after undergoing spinal anaesthesia. The other drugs namely tramdadol, pethidine etc. used presently treat shivering after it has occurred but they don't prevent it & they also interfere with respiration . Purpose

of this study is assessment of efficacy of dexmedetomidine in clinical settings and to have a better & safer alternative for the management of shivering.

Procedure Involved:

If you agree to enrol yourself in my study, I will ask your present past and family history. Then you will be clinically examined in detail and routine investigations like Hb, TC, DC, Platelet Count, RBS, Blood Urea, Serum Creatinine, Blood Grouping, Chest X-ray, ECG, will be done accordingly. You will be allotted into one of the two groups randomly using a computer generated software. One group will receive Inj.Dexmedetomidine and the other group will receive a placebo- which has no effect on shivering. This will be a double blinded procedure, where neither you nor me will know as to which group you have been allotted to. After the administration of the drug or placebo, if u still suffer from shivering, you will be treated with Inj.Tramadol 1µg/kg by intravenous route

Risks:

There is almost no risk involved with use of intravenous Dexmedetomidine. It may cause nausea, vomiting. Rarely may it cause allergic skin reactions, however, if there is a pre-existing liver insufficiency, dexmedetomidine can be toxic even in small doses.

Benefits:

It is an effective and safe anti shivering agent which can be used during spinal anaesthesia

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enrol yourself in this study. Your decision will not change present or future health care services offered to you at K.L.E. hospital.

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 are members of the research team. No information about you or 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 & MRC, Belgaum. There is no compensation or payment for such medical treatment by law. If you are injured you may contact Dr. Avinash Kumar Jha, at Department of Anaesthesiology, KLES Hospital& MRC or by Ph. No: 9845316624.

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 Dr. Avinash Kumar Jha, Department of Anaesthesiology, KLES Hospital and MRC, Belgaum, phone number: 9845316624. or Dr. Vandana Gogate$_{M.D.}$, Professor, Dept Of Anaesthesiology, KLES Hospital and MRC, Belgaum Ph: 9844083030.

If you have any queries about your rights as a study subject, you may call Dr. Ganga Pilli, Professor, Department of Pathology and Chairman, J.N. Medical College Institutional Ethical Committee for Human Subjects Research, Phonenumber- 9448863866, or extension 4052 at J.N. Medical College, Belgaum.

"Efficacy of dexmedetomidine as an anti-shivering agent following spinal anaesthesia in adults" –A one year Randomized placebo controlled trial.

Consent for participation in research trial

I, Mr/Ms/Mrs. _____ voluntarily agree for the participation 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 : _____

Signature or the Left Thumb Print of Subject : _____

Date :

Witness Name : _____ Signature:_____

Date :

Investigators Name: _____ Signature:_____

Date :

Place : _____

Annexures

Annexure II

ANNEXURE II – PROFORMA

TITLE- "EFFICACY OF DEXMEDETOMIDINE AS AN ANTI SHIVERING AGENT FOLLOWING SPINAL ANAESTHESIA IN ADULTS, A 1 YEAR DOUBLE BLINDED PLACEBO CONTROLLED RANDOMIZED TRIAL"

Name & Address of the patient:

_____

_____

Age of the Patient:_____ IP. No. _____

Weight of Patient: _____ Sex.

Anaesthesiologist: _____ Surgeon: _____

PREANAESTHETIC EVALUATION :

Chief Complaints:

Past History:

- History of Diabetes Mellitus/Hypertension/Asthma/Tuberculosis
- Drug Therapy:
- Previous Anaesthetic procedure/Previous surgeries:
- History of renal disease, hepatic disease and neurological diseases.

Family History

General Physical Examination:

Weight: Temperature: Pallor: Height

Cyanosis: Pedal Oedema: Clubbing:

Pulse : B.P : RR :

Airway Assessment:

Mouth Opening: Teeth:

Jaw movements: MP Grading:

SYSTEMIC EXAMINATION :

Cardiovascular System:

Respiratory System:

Per Abdomen:

Central Nervous system:

Spine assessment:

INVESTIGATIONS:

Hb%: Urine Routine:

Any Other:

ASA STATUS: Grade 1 / 2

Diagnosis:

Proposed Surgery:

Inclusion Criteria:

- 1. ASA physical status I and II.
- 2. Age between 18 to 60 years.
- 3. Infraumbilical surgeries done under Spinal anaesthesia with a minimum duration of 45 minutes to 1 hour

Exclusion Criteria:

- Patients not willing to give consent
- Allergic to the study drugs-bupivacaine and dexmedetomidine
- A Pre-Operative baseline temperature of more than 37.5 degree Celsius
- Patients on long standing opioids
- Patients suffering from thyroid disorders
- In surgeries like TURP, where irrigation fluids are used
- Patients who are known case of liver disease

Methodology:

After obtaining the approval of the Ethical committee and written informed consent, a total of 60 patients confirming to the inclusion and exclusion criteria will be included in the study.

Patients will be randomly divided into two groups, Group A who would be administered dexmedetomidine and Group B who would be administered 0.9 % normal saline, by using computer generated table. An investigator who was not otherwise involved in the study will prepare syringes containing saline or dexmedetomidine; thus, the study will be double-blinded The temperature of the operating room will be maintained at a constant temperature between 22 to 24 degree Celsius (measured by a wall thermometer).

Before performing spinal anaesthesia, each patient will receive 10 ml/kg of lactated Ringer's solution half an hour before spinal anaesthesia.

Following the guidelines for asepsis, subarachnoid anaesthesia will be instituted at the L3-4 interspace.

3 ml of hyperbaric bupivacaine will be injected using a 23G Quincke spinal needle, with bevel facing upwards.

Group A will be given an i.v. infusion of dexmedetomidine 1 µg/kg, administered by diluting 200 µg (2ml) of the drug diluted upto 50ml, resulting in a solution strength of 4 µg/ml. it will be administered using a syringe pump over a 20-min period. Group B will receive an equal volume of saline. After 10 minutes of administration of spinal anaesthesia, level of sensory blockade will be assessed using spirit swab, whereas motor blockade will be assessed by Modified Bromage scale as follows

0 = No Motor Block

1 = Can flex knee, move foot, but cannot raise leg

2 = Can move foot only

3 = Cannot move foot or knee

The patient's temperature will recorded every 15 minutes and continued up to 3 hours after giving the subarachnoid blockade, using a tympanic membrane temperature probe.

Intravenous fluids will be administrated at room temperature and given without inline warming. Supplemental oxygen (5l/min) will be delivered via a facemask during the operation.

All patients will be covered with one layer of surgical drapes over the chest, thighs, and calves during the operation and then one cotton blanket over the entire body. No other warming device will be used. A core temperature below 36˚C was considered hypothermia.

The presence of shivering will be assessed by a blinded observer after the completion of subarachnoid drug injection. Shivering will be graded on a scale:

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,

4 = shivering involving the whole body.

The incidence and severity of shivering will be recorded at 15-min intervals during the operation and in the recovery room. If score is three or greater Inj Tramadol 1mg/kg IV will be administered. Side effects, such as headache, allergy, hypotension, bradycardia, sedation, nausea and vomiting ,if any will be recorded.

If the patient's heart rate fell below 60 bpm, 0.6 mg atropine will be administered i.v.

Hypotension will be defined as a decrease in the mean arterial pressure (MAP) of more than 20 % from baseline. Hypotension will be treated with 6 mg mephenteramine via i.v. bolus and then with further i.v. infusion of lactated Ringer's solution as required.

If patients developed nausea and vomiting, ondansetron 0.08mg/kg will administered through the intravenous route.

At intervals of 15 minutes, the attending anaesthesiologist will assess the degree of sedation on 5-point scale:

1 = fully awake and oriented,

2 = drowsy,

3 = eyes closed but open on command,

4 = eyes closed but open to mild physical stimulation,

5= eyes closed and unresponsive to mild physical stimulation.

STATISTICAL ANALYSIS

All statistical data will analyzed by SPSS 11.0 Demographic and Parametric data will be analysed by student unpaired-t test. Non- parametric data will be analysed by using Mann Whitney Test. P value of less than 0.05 will be considered significant

Observations:

Readings recorded in the following manner:

DRUG Administered:_____.

Group:_____.

Variable	Preop	T15	T30	T45	T60	T75	T90
Temperature							
Shivering Scale							
Sedation							

Variable	T105	T120	T135	T150	T165	T180
Temperature						
Shivering Scale						
Sedation						

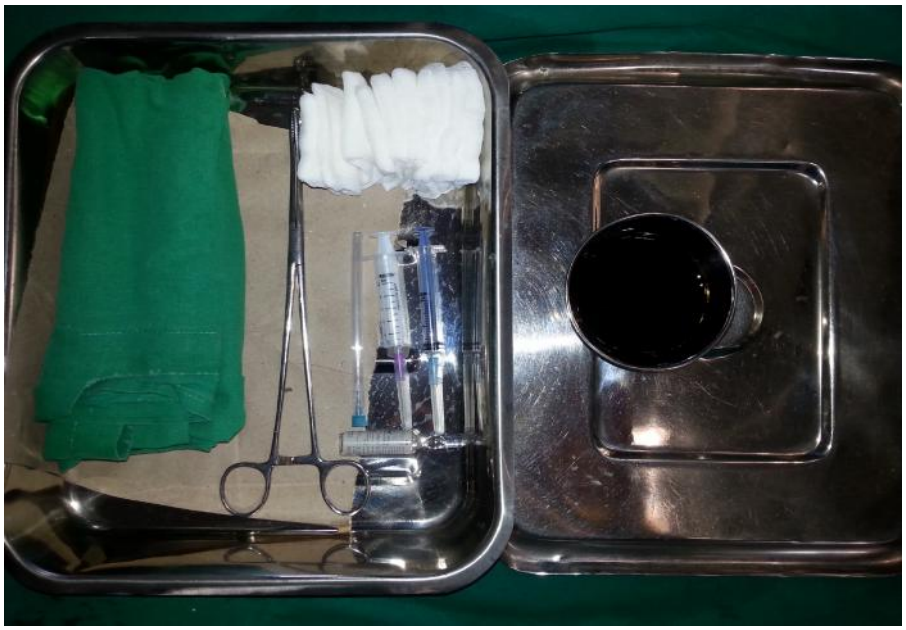
Side Effects –

Signature of staff in charge:

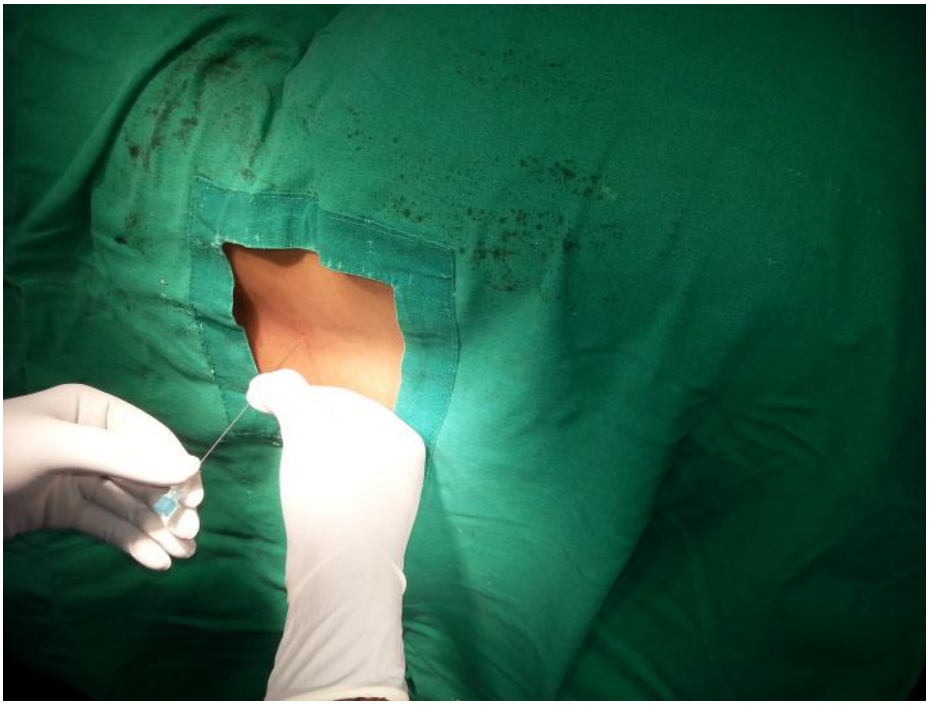
Annexures

Annexure III

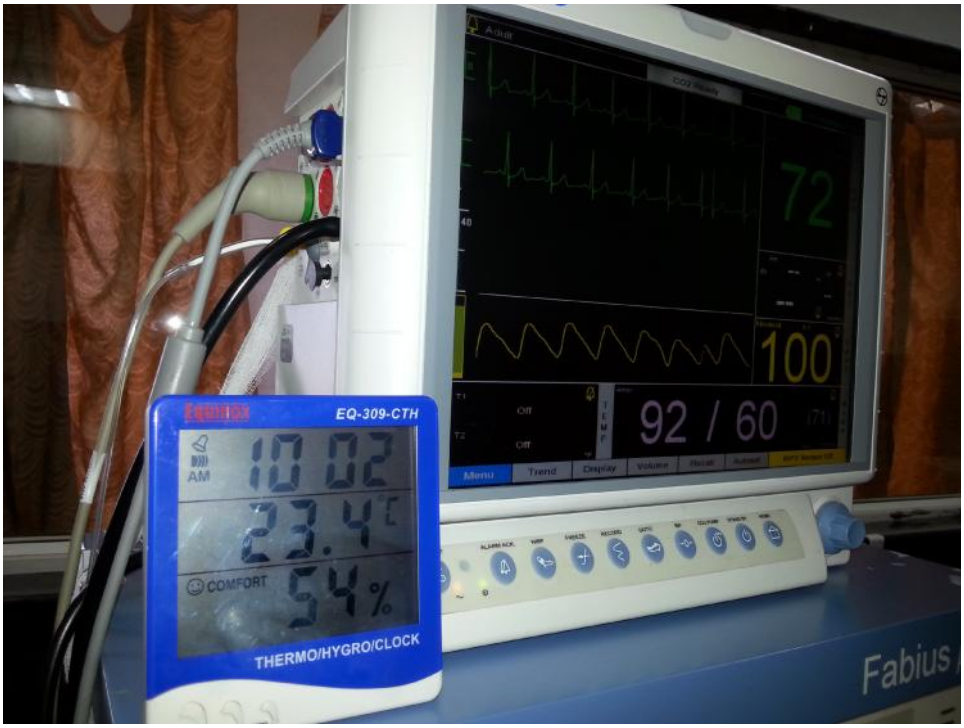
ANNEXURE III – PHOTOGRAPHS



PHOTOGRAPH 1 – DRUGS USED IN SPINAL ANAESTHESIA - showing povidone iodine, 0.5% Bupivacaine Heavy, 23 G Quincke needle, syringes



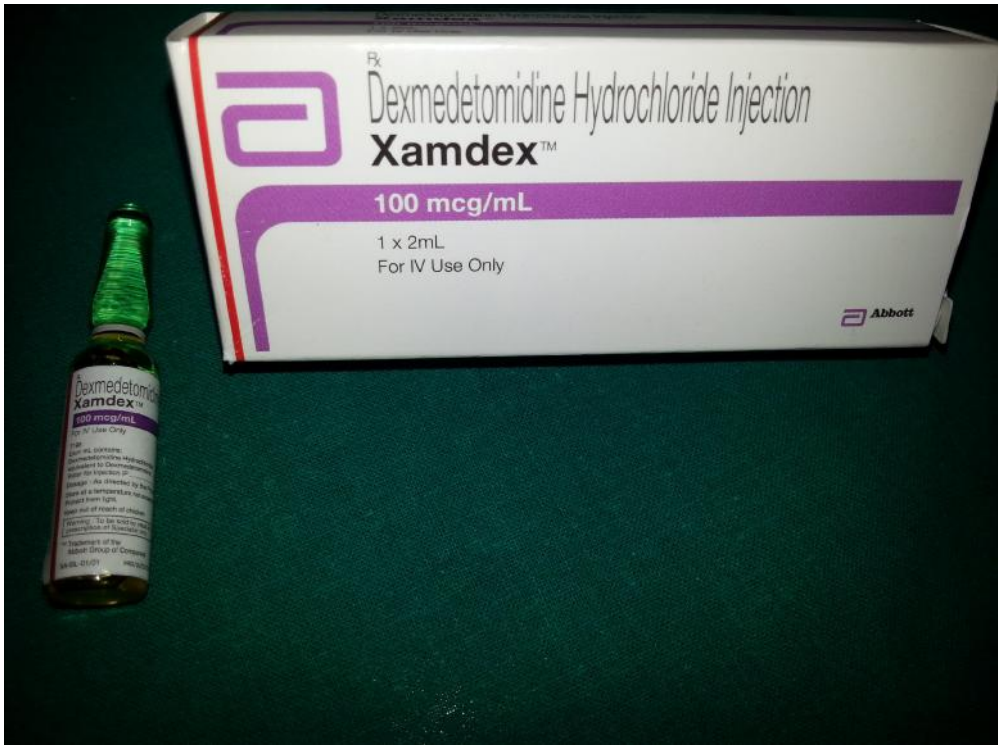
PHOTOGRAPH 2 – Administration of Spinal Anaesthesia, using 23G Quincke needle in left lateral position.



PHOTOGRAPH 3 – Room temperature monitoring along with ECG, Heart Rate, NIBP, SPO_2

PHOTOGRAPH 4 – Tympanic membrane temperature probe.

PHOTOGRAPH 5 – TRAMADOL



PHOTOGRAPH 6 – DEXMEDETOMIDINE

DEXMEDETOMIDINE																		
S.NO	IP NO.	AGE(Yrs)	SEX	HEIGHT(Cm)	WEIGHT(Kg)	BASELINE VALUES			TEMPERATURE (DEGREE CENTIGRADE)									
						HR	SBP	DBP	PRE OP	T15	T30	T45	T60	T75	T90	T105	T120	T135
1	566455	47	MALE	152	60	62	130	70	36.7	35.3	35	35.2	35.4	35.8	36.3	36.6	36.7	36.7
2	550374	45	MALE	152	59	82	126	72	36.7	36.1	35.3	35.3	35.4	35.4	35	36	36.3	36.6
3	547054	28	FEMALE	155	55	80	120	80	36.6	35.6	35	35.1	35.2	36	36.1	36.3	36.4	36.4
4	567215	40	FEMALE	170	82	83	138	60	36.6	35.4	35.4	35.2	35.4	35.8	36.2	36.3	36.4	36.6
5	552310	35	FEMALE	153	54	76	118	72	36.7	35.4	35.1	35.3	35	36	36.2	36.3	36.6	36.6
6	552284	25	MALE	146	61	80	114	82	36.6	36	35.4	35.5	35.8	36.1	36.3	36.4	36.6	36.5
7	550706	36	MALE	153	49	76	114	70	36.6	35.8	35.4	35.3	35.7	36	36.5	36.6	36.5	36.6
8	566956	24	MALE	166	69	82	118	84	36.6	35.7	35	35.1	34.9	35.3	35.9	36	36.3	36.4
9	552892	33	FEMALE	166	70	90	130	76	36.8	36	35.1	35.8	34.9	36.2	36.3	36.4	36.7	36.8
10	561785	35	MALE	157	55	70	130	68	36.7	35.3	35.1	35	35.3	36.2	36.7	36.6	36.7	36.7
11	554457	42	FEMALE	157	49	70	136	76	36.6	35.3	35.6	35.3	36	36.1	36.1	36.3	36.5	36.6
12	554713	55	MALE	151	57.5	62	140	68	36.7	35.2	35	35.2	35.1	35.8	35.9	36	36.1	36.5
13	530975	32	MALE	168	60	62	114	70	36.6	35.2	35.1	35.2	35.2	35.2	35.4	35.4	35.9	35.8
14	552477	36	FEMALE	144	61	84	128	72	36.6	35.6	35.1	35.1	35.3	35.3	36	36.1	36.3	36.5
15	564964	49	FEMALE	163	70	86	136	70	36.6	36	35	35.8	35	35.8	36	36.4	36.5	36.5
16	553572	35	MALE	157	52	98	130	80	36.7	35	35	34.9	35.4	35.9	36.4	36.7	36.6	36.6
17	568199	35	FEMALE	159	64	80	140	86	36.6	35.3	35.1	35.2	35.4	35.7	36	36.2	36.3	36.5
18	567423	42	FEMALE	169	90	65	118	82	36.7	35.7	35.3	35.1	35.4	35.4	36	36.1	36.4	36.6
19	553145	45	MALE	149	59	79	126	82	36.7	36	35.1	35.8	35.2	35.8	36	36.3	36.6	36.6
20	567624	46	MALE	170	82	66	132	82	36.6	35.8	35.1	35.2	36	36.1	36.2	36.4	36.5	36.4
21	554605	38	MALE	171	76	80	132	70	36.7	35.9	35.3	35.4	35.3	35.9	36	36	36.3	36.6
22	554206	31	FEMALE	168	68	84	132	82	36.7	35.8	35.4	35.4	35.5	36.1	36.2	36.5	36.6	36.5
23	552365	25	MALE	149	54	68	126	82	36.6	36	35.7	35.8	35.1	35.6	35.8	36.3	36.5	36.6
24	531032	35	FEMALE	160	55	69	118	90	36.5	35.1	35.1	35.3	36.1	36.1	36.3	36.4	36.5	36.6
25	552552	34	MALE	158	60	70	110	68	36.8	35.7	35.1	35.5	35.1	35	35.8	35.9	36.2	36.5
26	553226	55	MALE	169	81	60	142	88	36.8	36	35.5	35.7	35.1	35.2	35.6	35.9	36.4	36.4
27	551824	33	FEMALE	160	60	80	128	68	36.7	35.8	35.1	35.3	35.2	35.5	35.6	36.3	36.6	36.6
28	552285	48	MALE	55	120	76	120	76	36.8	36.1	35.4	36	35.3	35.9	36.2	36.3	36.6	36.5
29	567796	32	MALE	161	65	80	128	82	36.6	35.4	35	35	35.1	35.4	35.5	36	36.1	36.2
30	566575	35	FEMALE	148	56	69	132	70	36.6	35.8	35.3	35.8	35.4	35.5	35.9	36.3	36.4	36.6
MEAN		37.7	17/ 13	155.2	65.11666667	75.63333	126.8667	75.93333	36.66	35.64333	35.20333	35.36	35.34	35.73667	36.01333	36.24333	36.43667	36.52
S.D.		8.217517		20.5349156	14.67444608	9.219482	8.434695	7.220034	0.077013									

			SHIVERING	SEDATION													BRADYCARDIA
T150	T165	T180	ONSET(MINUTES)	PRE OP	T15	T30	T45	T60	T75	T90	T105	T120	T135	T150	T165	T180	
36.7	36.7	36.7	NO	1	2	2	3	3	2	2	2	1	1	1	1	1	1
36.7	36.6	36.7	NO	1	2	3	3	3	2	2	2	1	1	1	1	1	NO
36.5	36.5	36.5	NO	1	2	3	3	3	3	3	3	2	2	1	1	1	NO
36.6	36.6	36.6	25	1	1	2	2	1	1	1	1	1	1	1	1	1	NO
36.6	36.6	36.6	NO	1	1	2	2	3	3	3	2	2	1	1	1	1	NO
36.6	36.6	36.6	NO	1	1	2	2	2	2	1	1	1	1	1	1	1	1
36.6	36.6	36.6	NO	1	2	3	2	2	2	1	1	1	1	1	1	1	NO
36.6	36.6	36.6	NO	1	2	2	2	2	3	2	2	2	1	1	1	1	NO
36.7	36.7	36.7	NO	1	3	3	3	3	3	2	2	1	1	1	1	1	1
36.7	36.7	36.7	NO	1	2	2	2	2	2	1	1	1	1	1	1	1	NO
36.6	36.6	36.6	NO	1	1	2	2	2	3	3	2	2	2	1	1	1	1
36.6	36.6	36.7	NO	1	1	1	2	2	2	2	2	2	1	1	1	1	NO
35.8	36.2	36.5	NO	1	1	2	2	2	2	1	1	1	1	1	1	1	NO
36.6	36.6	36.6	32	1	2	2	1	1	1	1	1	1	1	1	1	1	1
36.6	36.6	36.6	NO	1	1	2	2	3	3	3	3	2	2	1	1	1	NO
36.7	36.7	36.6	23	1	2	1	1	1	1	1	1	1	1	1	1	1	NO
36.6	36.6	36.6	NO	1	1	2	2	2	2	1	1	1	1	1	1	1	NO
36.6	36.7	36.7	NO	1	1	2	3	2	2	2	1	1	1	1	1	1	1
36.6	36.6	36.6	NO	1	3	3	3	3	2	2	1	1	1	1	1	1	1
36.6	36.6	36.6	NO	1	1	2	2	3	3	2	2	1	1	1	1	1	NO
36.6	36.6	36.6	NO	1	2	2	2	2	2	2	2	1	1	1	1	1	NO
36.6	36.7	36.7	NO	1	1	1	2	2	3	3	2	2	1	1	1	1	NO
36.6	36.6	36.6	NO	1	3	3	3	2	2	2	1	1	1	1	1	1	NO
36.5	36.5	36.5	NO	1	1	2	2	2	3	2	1	1	1	1	1	1	NO
36.6	36.8	36.8	NO	1	2	3	3	3	3	3	3	2	2	1	1	1	NO
36.6	36.8	36.7	NO	1	1	3	3	3	3	2	2	2	2	1	1	1	1
36.6	36.6	36.6	NO	1	2	3	3	2	2	2	2	1	1	1	1	1	NO
36.8	36.7	36.8	NO	1	3	2	2	2	2	1	1	1	1	1	1	1	1
36.5	36.6	36.6	NO	1	2	2	3	3	3	2	2	1	1	1	1	1	NO
36.6	36.6	36.6	NO	1	2	3	3	3	3	3	2	2	1	1	1	1	NO
36.59	36.62	36.63	26.66	1	2	2	2	2	2	2	2	1	1	1	1	1	TOTAL = 9

ASA	DURATION
1	88
1	34
1	62
1	94
1	143
1	50
1	147
1	149
1	101
2	118
2	135
1	92
1	38
2	124
2	85
1	78
1	91
1	125
2	138
1	90
1	89
1	68
1	58
1	36
1	82
1	37
1	83
1	94
1	77
1	62
25 AND 5	88.9333333
	34.1668657

Annexures

Annexure IV

ANNEXURE IV – MASTER CHART

ASA	-	American Society of Anaesthesiologist
Cm	-	Centimeter
DBP	-	Diastolic Blood Pressure
F	-	Female
HR	-	Heart Rate
IP NO.	-	In Patient Number
Kg	-	Kilograms
M	-	Male
PRE OP	-	Pre Operative Temperature
S.NO	-	Serial Number
SBP	-	Systolic Blood Pressure
S.D.	-	Standard Deviation
Yrs	-	Years