"A PROSPECTIVE, RANDOMIZED CLINICAL TRIAL FOR COMPARISON OF PETHIDINE AND DEXMEDETOMIDINE FOR THE CONTROL OF INTRAOPERATIVE SHIVERING UNDER SPINAL ANAESTHESIA"

By

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Synopsis submitted to the

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IN

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Under the guidance of

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LIST OF ABBREVIATIONS USED

(in alphabetical order)

ASA	: American society of anaesthesiologists
BP	: Blood pressure
CNS	: Central nervous system
CO_2	: Carbon dioxide
COX	: Cyclooxygenase
DBP	: Diastolic blood pressure
EtCO2	: End-tidal carbon dioxide
FRC	: Functional residual capacity
HR	: Heart rate
H/h	: Hours
IAP	: Intra-abdominal pressure
IV	: Intravenous
IVPCA	: Intravenous patient controlled analgesia
IVRA	: Intravenous regional anaesthesia
MAP	: Mean arterial pressure
Na	: Sodium
NMDA	: N-methyl-d-aspartic acid
NO	: Nitric oxide
N_2O	: Nitrous oxide
No.	: Number
NSAID's	: Non steroidal anti inflammatory drugs
NS	: Normal Saline
PABA	: P-amino- benzoic acid

PaCO2	: Partial pressure of arterial carbon dioxide
PACO2	: Partial pressure of alveolar carbon dioxide
PACU	: Post anaesthesia care unit
PCEA	: Patient controlled epidural analgesia
PONV	: Post-operative nausea & vomiting
PR	: Pulse rate
RR	: Respiratory rate
SB	: Systolic blood pressure
SPET	: Single positron emission tomography
SPSS	: Statistical presenting system software
TENS	: Transcutaneous electrical nerve stimulation
VAS	: Visual analogue scale
VRS	: Verbal rating scale
WDR	: Wide dynamic range neurons

ABSTRACT

A PROSPECTIVE, RANDOMIZED CLINICAL TRIAL FOR COMPARISON OF PETHIDINE AND DEXMEDITOMEDINE FOR THE CONTROL OF INTRAOPERATIVE SHIVERING UNDER SPINAL ANAESTHESIA

Background and Aims:

Pharmacological methods using variety of drugs like Pethidine, Morpine, Tramadol, Clonidine, Doxapram, Ketansarine, Neofam, Neostigmine, Magnesium sulfate have been tried in post spinal shivering.

In the quest for more safe and efficacious drug, in our study, we compared two easily available and safe drugs Dexmedetomidine and Pethidine, intravenously administered for treating shivering in patients who received spinal anaesthesia for various surgical procedures.

OBJECTIVES OF THE STUDY:

1) Time from drug administration to control of shivering

2) Recurrence of shivering after administration of drug

3) Adverse effects

4) Hemodynamic changes

Methods:

A prospective, randomised, study was conducted in 80 ASA I and II patients of either gender, aged between 20 and 60 years, scheduled for various surgical procedures under spinal anaesthesia. The patients were randomised in two groups of 40 patients each to receive either dexmedetomidine 0.5mcg/kg or pethidine 0.5 mg/kg

as a slow intravenous bolus over 5 minutes. Grade of shivering, onset of shivering, time for control of shivering, disappearance of shivering, recurrence, and adverse effects were observed at scheduled intervals.

Results:

Time taken for cessation of shivering was 205.3±18.1 (sec) for dexmedetomidine and 413±16.8 (sec) for pethidine with ("p" value - 0.00). Nausea and recurrence of shivering was observed only in pethidine group. The sedation profiles of both the drugs are comparable.

Conclusion:

We conclude that although both drugs are effective, the time taken for cessation of post-spinal shivering is less with dexmedetomidine when compared to pethidine Moreover, dexmedetomidine has negligible adverse effects, whereas pethidine is associated with significant nausea and recurrence of shivering.

INDEX

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

Regional anaesthesia (spinal anaesthesia) is widely used as a safe anesthetic technique for both elective and emergency operations. Shivering is known to be a frequent complication, reported in 40 to 70% of patients undergoing surgery under regional anaesthesia [1, 2].

Shivering besides being physiologically stressful to the patient also causes unpleasant to the anesthesiologists and surgeons. Shivering can occur in patients receiving regional anaesthesia as well as those patients recovering from general anaesthesia. The main physiology of shivering is to provide heat, but its occurrence in relation to anaesthesia is inconsistent and incompletely understood. Shivering can be very unpleasant and physiologically stressful for the patients. It causes several undesirable physiologic consequences including increase in oxygen consumption, hypercarbia and increase in minute ventilation. It induces arterial hypoxemia, lactic acidosis, increased intra-ocular pressure, intracranial pressure and interfere with patient monitoring [2]. Shivering may negate orthopedic procedures like fractures and dislocations and may also cause damage to dental prosthesis [3].

Spinal anaesthesia is known to decrease the vasoconstriction and shivering thresholds. There is core to periphery redistribution of heat due to spinal induced vasodilatation and shivering is preceded by core hypothermia and vasoconstriction above the level of block. [2, 4]

Interestingly, core hypothermia following spinal anaesthesia may not trigger sensation of cold as cutaneous vasodilatation resulting from sympathetic blockade

increases skin temperature leading to a sensation of warmth although accompanied by thermoregulatory shivering.[5]

Various methods are available for the control of shivering during anaesthesia. These may be non-pharmacological and pharmacological. Intraoperative hypothermia can be minimized by any technique that limits cutaneous heat loss to the environment such as those due to cold operating room, evaporation from surgical incisions and conductive cooling produced by administration of cold intravenous fluids. Fluid warmers [6], ambient operation theater temperature, space blankets [7], surgical drapes and active circulating water mattress have been used in Non-pharmacological methods, to maintain normothermia these are effective but may be expensive and are not practical in all the settings. Pharmacological methods using various drugs like Tramadol [8, 9], Clonidine, Doxapram, Dexmedetomidine, Pethidine, Nefopam, Neostigmine, Magnesium sulphate [10] have been tried.

In the quest for more safe and efficacious drug in our study, we compared two effective and safe drugs Dexmedetomidine and Pethidine, intravenously administered for treating shivering in patients who received spinal anaesthesia for various surgical procedures.

AIMS AND OBJECTIVES

To compare the efficacy of two drugs 0.5mcg/kg of Dexmedetomidine and 0.5mg/kg of Pethidine with respect to

1) Time from drug administration to control of shivering
2) Recurrence of shivering after administration of drug
3) Adverse effects
4) Hemodynamic changes

REVIEW OF LITERATURE

1) **ADITI A. DHIMAR (2007)** [8] conducted a study comparing the relative efficacy of intravenous administered Tramadol against Pethidine to control intra-operative and post-operative shivering in 60 ASA grade 1-3 patients undergoing central neural blockade. They noted the incidence of shivering was high as 40%-60% in patients who received a central neural block. All patients were assessed for shivering grades, its disappearance, hemodynamic status and complications. Axillary temperature was noted at the time when shivering appeared, and at regular intervals thereafter. Either drug was used intravenously in dose of 1mg/kg body weight for patients in their respective study group. The onset of disappearance of shivering took 1 minute in Tramadol group while 3 minutes in Pethidine group. Complete disappearance of shivering occurred in 5 minutes in Tramadol group while 20 minutes in Pethidine group. Thus, they concluded that Tramadol was effective in controlling shivering and that it was qualitatively superior to Pethidine.

2) **Zahedi. H (2004); 5: 235-239.** [11] Conducted a study in 2004 for comparing the effect of Tramadol and Pethidine for post anaesthetic shivering. This double-blind clinical trial was performed on 300 patients who underwent general anaesthesia for elective cataract surgery. Intravenous Tramadol 1mg/kg or Pethidine 0.5mg/kg was administered to subjects who developed post anaesthetic shivering. They were monitored in the recovery room for 1 hour. Cessation time of shivering, recurrence of the event, duration of recovery, respiratory depression, nausea, vomiting and arterial O2 saturation was recorded. One hundred and twenty patients (40%) had post anaesthetic

shivering. In the Tramadol group, shivering terminated within minutes after injection (mean 5 min). They did not have recurrence of shivering, respiratory depression, reduction in spo2 and nausea or vomiting during recovery. In the Pethidine group, shivering terminated within 13 minutes (mean 9 min) after injection, but in 10 patients it recurred after 30 minutes. In this group 28 patients had respiratory depression, reduction in spo2, nausea and vomiting. They concluded that Tramadol is superior to Pethidine as it induced a faster termination of post anaesthetic shivering and did not entail adverse effects on the respiratory system and spo2, recurrence of shivering or nausea and vomiting. Easy availability and minimum monitoring requirements are other advantages of Tramadol.

3) **Geeta Mittal, Kanchan Gupta, Sunil Katyal, Sandeep Kaushal(2016)** [(13)] A prospective, randomized, and double‐blind study was conducted in 50 American Society of Anesthesiologists Grade I and II patients of either gender, aged between 18 and 65 years, scheduled for various surgical procedures under spinal anaesthesia. The 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. Grade of shivering, onset of shivering, time for cessation of shivering, recurrence, response rate, and adverse effects were observed at scheduled intervals. Unpaired *t*‐test was used for analyzing the data. 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). There was not much difference in the sedation profile of both the drugs. We conclude 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.

4) **Hatem Saber Mohamed(2015)** [14] A prospective, randomized, double-blind, controlled study was conducted on 100 ASA grade I and II patients of either sex, aged 18–60 years, scheduled for elective lower abdominal and lower limb surgeries, under spinal anesthesia. Patients who developed post-spinal anesthesia shivering of grade 3 or 4 were included in the study, and randomly allocated to one of two groups, group D (n= 50), received Dexmedetomidine in a dose of 0.5 mcg/kg diluted in 10 ml isotonic saline slowly I.V. (one minute duration), and group N (n=50), received Nefopam in a dose of 0.15 mg/kg diluted in 10 ml isotonic saline slowly I.V. (one minute duration) when shivering was observed. Time taken for control of shivering, response rate, recurrence rate, hemodynamics, time to first request of rescue analgesic, one-patient cost and adverse effects were recorded. The time taken for control of shivering was statistically significantly shorter in Nefopam group (group N) compared with Dexmedetomidine group (group D). The average time taken for disappearance of shivering was 2.35 ± 0.67 min in group N compared with group D (4.63 ±1.19 min) (p= 0.041). Patients with incomplete response were more in group D (two patients in group D compared with nil in group N), but not statistically significant and recurrence rate was one patient in group D compared with nil in group N. Time to first request to rescue analgesic was significantly prolonged in group N (351.24 ± 19.71 min) compared with group D (192.63 ± 9.08 min). Adverse effects such as bradycardia, hypotension and sedation were observed in Dexmedetomidine group, while pain at injection

was noted in Nefopam group. Conclusion: Nefopam is better as compared to Dexmedetomidine for control of intraoperative shivering under spinal anesthesia due to its rapid onset, higher response rate, no sedation, lesser hemodynamic alterations, lesser requirements of rescue analgesics and lesser costs.

5) **Lim Fern and Karis Misiran (2015)** [15] study was performed to compare the effectiveness of intravenous Dexmedetomidine with that of Pethidine and tramadol in the treatment of post-neuraxial anaesthesia shivering. One hundred and two patients of both genders, aged 18–70 years with American Society of Anesthesiologists physical status I and II undergoing spinal or combined spinal and epidural anaesthesia for elective surgery were enrolled in this study. Sixty of them developed shivering after an intrathecal injection of 0.5% hyperbaric Bupivacaine 15 mg. They were then randomly allocated to receive either intravenous Dexmedetomidine 0.5 μg/kg, Pethidine 0.5 mg/kg or tramadol 0.5 mg/kg. The response rate to treatment, the degree of sedation and the side-effects were recorded. The response rate to treatment was highest in the Dexmedetomidine group, and it was only significant when compared to tramadol group ($p = 0.0012$). It was noted that the response rate was higher in the Pethidine than in the tramadol group. This difference was not statistically significant ($p = 0.082$). The sedation score post treatment was similar in all three groups, but more patients in the Dexmedetomidine group developed hypotension and bradycardia ($p < 0.05$). Conclusion: Dexmedetomidine 0.5 μg/kg was more effective than tramadol 0.5 mg/kg and Pethidine 0.5 mg/kg, and both tramadol and Pethidine were found to have similar efficacy, in the

treatment of post-neuraxial anaesthesia shivering. However, Dexmedetomidine caused a higher incidence of hypotension and bradycardia.

6) **MAHESH, LAVANYA KAPARTI** [16] A Randomised Trial was conducted on forty patients of ASA 1 and 2 status posted for elective surgical procedures under neuraxial block were selected. Group P (n=20) received Pethidine 0.5mg/kg IV and group T (n=20) received tramadol 1.0 mg/kg IV. There was no significant difference found in the axillary temperature as well as shivering grades at the start of study between the two groups. Shivering disappeared in all the patients (20) of group T by two minutes but in group P disappearance of shivering was achieved at end of five minutes. The time interval between administration of drug after onset of shivering and disappearance of shivering was significantly shorter in the Tramadol group. Both the drugs were found to be effective in reducing shivering. Nineteen patients in the Group T had control of shivering at end of five minutes but there were no patients who had control of shivering Group P ($p < 0.0001$) which is statistically significant. There was no statistically significant difference with respect to heart rate, mean blood pressure and axillary temperature between the two groups. The incidence of recurrence of shivering was 50% in pethidine group while only in 10% in tramadol group. Complications like nausea and vomiting occurred in 40% in pethidine group while 5% in tramadol group. The difference is statistically significant. Tramadol reduced the occurrence of postanesthetic shivering more significantly than pethidine.

7) **RAJAGOPALAN VENKATRAMAN** [17] et al conducted a prospective, randomized, double blinded control study on 90 patients who developed shivering under spinal anaesthesia. They were randomly allocated into three groups with Group T receiving tramadol 1 mg.kg−1, Group C getting clonidine 1 mcg.kg−1 and Group D patients receiving dexmedetomidine 0.5 mcg.kg−1. The time taken to control shivering, recurrence rate, hemodynamic variables, sedation score and adverse effects were observed. Dexmedetomidine was faster in the control of shivering in 5.7 ± 0.79 minutes (min) whereas tramadol took 6.76 ± 0.93 min and clonidine was slower with 9.43 ± 0.93 min. The recurrence rate was much lower in the dexmedetomidine group with 3.3% than for cloni-dine (10%) and tramadol (23.3%) group. The sedation achieved with dexmedetomidine was better than clonidine and tramadol. The tramadol group had more cases of vomiting (four) and dexmedetomidine group had six cases of hypotension and two cases of bradycardia. Two of the clonidine patients encountered bradycardia and hypotension. Dexmedetomidine is better than tramadol and clonidine in the control of shivering because of its faster onset and less recurrence rate. Though complications are encountered in the dexmedetomidine group, they are treatable.

8) **BURHANETTIN USTA** [18] **et al** conducted a study to evaluate the effect of dexmedetomidine on shivering during spinal anaesthesia. Sixty patients (American Society of Anaesthesiologists physical status I or II, aged 18-50 years), scheduled for elective minor surgical operations under spinal anaesthesia with hyperbaric bupivacaine, were enrolled. They were

administered saline (group C, n = 30) or dexmedetomidine (group D, n = 30). Motor block was assessed using a Modified Bromage Scale. The presence of shivering was assessed by a blinded observer after the completion of subarachnoid drug injection. Hypothermia was observed in 21 patients (70%) in group D and in 20 patients (66.7%) in group C (p = 0.781). Three patients (10%) in group D and 17 patients (56.7%) in group C experienced shivering (p = 0.001). The intensity of shivering was lower in group D than in group C (p = 0.001). Time from baseline to onset of shivering was 10 (5-15) min in group D and 15 (5-45) min in group C (p = 0.207). Dexmedetomidine infusion in the perioperative period significantly reduced shivering associated with spinal anaesthesia during minor surgical procedures without any major adverse effect during the perioperative period. Therefore, we conclude that dexmedetomidine infusion is an effective drug for preventing shivering and providing sedation in patients during spinal anaesthesia.

9) **SUKHMINDER JIT SINGH BAJWA** [19] et al conducted randomized prospective study Reduction in the incidence of shivering with perioperative dexmedetomidine study was carried out on 80 patients, in American Society of Anaesthesiologists I and II, aged 22–59 years, who underwent general anaesthesia for laparoscopic surgical procedures. Patients were allocated randomly into two groups: group N (*n* = 40) and group D (*n* = 40). Group D were administered 1 µg/kg of dexmedetomidine intravenously, while group N received similar volume of saline during peri-op period. Cardiorespiratory parameters were observed and recorded during the preop, intraop, and postop periods. Any incidence of postop shivering was observed and recorded as per

4 point scale. Side effects were also observed, recorded, and treated symptomatically. Statistical analysis was carried out using statistical package for social sciences (SPSS) version 15.0 for windows and employing ANOVA and chi-square test with post-hoc comparisons with Bonferroni's correction. The two groups were comparable regarding demographic profile ($P > 0.05$). Incidence of shivering in group N was 42.5%, which was statistically highly significant ($P = 0.014$). Heart rate and mean arterial pressure also showed significant variation clinically and statistically in group D patients during the postop period ($P = 0.008$ and 0.012). A high incidence of sedation ($P = 0.000$) and dry mouth ($P = 0.000$) was observed in group D, whereas the incidence of nausea and vomiting was higher in group N ($P = 0.011$ and 0.034). Dexmedetomidine seems to possess antishivering properties and was found to reduce the occurrence of shivering in patients undergoing general anaesthesia.

10) **SUMAN SAINI, PARUL MULLICK** [20] conducted a comparative evaluation of Butorphanol with pethidine for treatment of post spinal shivering. 60 patients of asa I and II, aged 18–60yrs belonging to either sex, scheduled for elective surgery under spinal anaesthesia were included in the study. Patients were randomly allocated to three groups of twenty each to receive either pethidine 25mg (Group A), Butorphanol 1 mg (Group B) or normal saline 0.9% (Group C) in equal volume, on occurrence of shivering. It was observed that the mean response time was significantly less in Group B (1.59±0.79min) compared to Group A (3.83±1.7min) and Group C (13.53±1.5min). Success rate of Butorphanol (Group B) was 95% compared to pethidine (Group A) 85% and saline (Group C) 15%. Relapse of shivering was observed more in patients of Group A (11.7%) as compared to Group B

(5.3%) while shivering reappeared in all the patients who responded to saline treatment. Among the side effects, nausea was seen only in Group A (10%) while sedation was found more with group B (20%) compared to Group A (10%) and Group C(0%). Butorphanol is better than pethidine for control of post spinal shivering with more rapid response and lesser recurrence rate but is more sedating.

11) **P. SINGH, V. DIMITRIOU, R. P. MAHAJAN AND A. W. A. CROSSLEY** [21] conducted a double-blind comparison between doxapram and pethidine in the treatment of post an aesthetic shivering. Sixty patients who shivered after routine surgery under general anaesthesia were allocated randomly to receive normal saline (n = 20), doxapram 1.5mgkg-' (n = 20) or pethidine 0.33 mg kg1 (n = 20). Both doxapram and pethidine were effective in treating postoperative shivering 2-3 min after i. v. administration. In the group who received normal saline, 15 patients were still shivering 10 min after treatment, whilst in the doxapram group only three patients were shivering at that time. In the pethidine group, all patients had stopped shivering by 7 min after treatment. We conclude that both doxapram and pethidine were effective in the treatment of postoperative shivering.

12) **Asif Iqbal** [22] et al conducted a randomized control trial of Prophylactic Granisetron Vs Pethidine for the Prevention of Postoperative Shivering in Ninety patients aged 20-60yrs, ASA physical status I and II, scheduled for laparoscopic surgery under general anaesthesia were randomly allocated to receive either normal saline (Group S, n=30) as negative control, pethidine 25mg (Group P, n=30) as positive control or granisetron 40mcg.kg-1 (Group

G, n=30) intravenously before induction. The anaesthesia was induced with fentanyl 2mcg.kg-1, propofol 2mg.kg-1 and atracurium 0.5mg.kg-1 and maintained with sevoflurane 1-1.5%. Nasopharyngeal temperature was measured throughout the procedure. An investigator, blinded to the treatment group, graded postoperative shivering in a scale of 0 to 4. (0= no shivering, 1= piloerection or peripheral vasoconstriction but no visible shivering, 2= muscle activity in only one muscle group 3= muscle activity in more than one muscle group, 4= shivering involving the whole body). Prophylaxis was regarded as ineffective if shivering was greater than grade 3 and intravenous pethidine 25 mg was administered as rescue medication. The three groups did not differ significantly regarding patient characteristics. The numbers of patients shivering on arrival in the recovery room at 15 minutes after operation were significantly less in Group P (7%) and Group G (17%) than in Group S (60%). Groups P and G differ significantly than in Group S (p<0.05).However, the difference between Groups P and G was not statistically significant (p>0.05). The prophylactic use of granisetron (40mcg.kg-1) and pethidine (25mg) intravenous were found to be effective in preventing postoperative shivering.

13) **A Seifi** [23] et al conducted a randomised double blind comparative study of the effect of tramadol and pethidine on postoperative shivering 60 patients with ASA class 1 or 2, who developed postoperative shivering in recovery room. Half of them were treated with pethidine 0.5 mg/kg and others with tramadol 1 mg/kg. We compared the efficacy of tramadol with that of pethidine and the grade of shivering observed 5 minutes after injection of drug and categorized the patients to three groups; completely improved, partially improved and not improved that the last group had no improvement after 15 minutes. In this

study 16 from 30 patients improved completely with pethidine (53.3%) and 20 from 30, improved completely with tramadol (66.66%). Besides 6.66% of tramadol group and 20% of pethidine group had no improvement. Evaluating this complex data with Chi-Square test showed no significant difference between two drugs in stopping post-operative shivering (PV=0.294). In this study they found that there is no significant difference in anti-shivering effect of pethidine and tramadol although some papers believe that tramadol is superior and the others say that pethidine is most efficacious. This discrepancy could be due to difference in age of patients, duration of operation, core and room temperature in various studies.

ANATOMY

The spinal cord is the lower part of the central nervous system responsible for establishing contact between the brain in the cranial cavity and the peripheral end organs. [12] It occupies the upper two thirds of the spinal canal which is composed of the vertebral bones and fibro-cartilaginous intervertebral discs. There are 7 cervical, 12 thoracic and 5 lumbar vertebrae. The sacrum is a fusion of 5 sacral vertebras and there are small rudimentary coccygeal vertebras. The spinal column usually forms a double C, being convex anteriorly in the cervical and lumbar regions. The spinal canal contains the spinal cord with its coverings the meninges, fatty tissue and a venous plexus. Just like the brain, the spinal cord is also bathed in the cerebrospinal fluid (CSF), the volume of which is about 150ml, and correlates well with the changes in body habitus and weight of the patient. [24]

The spinal cord extends from the foramen magnum to the level of L1 in adults and L3 in children. The lower end is conical and is called the conus medullaris. The apex of the conus is continued down as the filum terminale [25]. Dural puncture above these levels is associated with a risk of damaging the spinal cord. An important landmark is that line joining the top of the iliac crests at L4 to L4/L5 vertebra. The pia mater is a highly vascular membrane which closely invests the spinal cord and the brain. The arachnoid membrane is a delicate, non-vascular membrane closely attached to the outermost layer, the dura. The arachnoid functions as the principle blood-brain barrier. [26]

The spinal cord gives off 31 pairs of spinal nerves. A dural sheath invests most nerve roots for a small distance after they exit the spinal canal. The dorsal (sensory) roots are generally larger than the anterior (motor) roots. [24,26]

The structures that the spinal needle will pierce before reaching the CSF are –

- The skin
- Subcutaneous fat
- Supraspinous ligament which joins the tips of the spinous processes together
- The interspinous ligament which is a thin flat band of ligament running between the spinous processes
- The ligamentum flavum which is quite thick and mostly composed of elastic tissue and runs vertically from lamina to lamina
- The epidural space which contains fat and blood vessels
- The dura
- The subarachnoid space which contains the spinal cord and nerve roots surrounded by CSF.

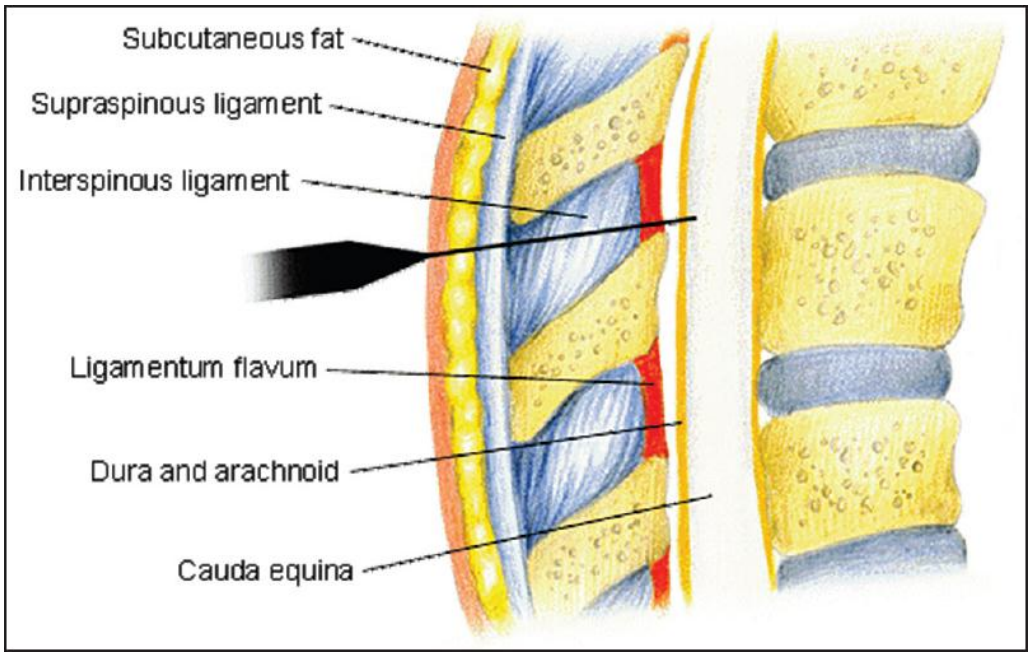


Fig : Anatomy of spinal cord

Physiology of Spinal Anaesthesia

The principal site of action for spinal anaesthesia is the nerve root. Local anaesthetic solution injected into the subarachnoid space blocks conduction of impulses along all nerves with which it comes in contact, although some nerves are more easily blocked than others.

There are three classes of nerve - motor, sensory and autonomic. The motor convey messages for muscles to contract and when they are blocked, muscle paralysis results. Sensory nerves transmit sensations such as touch and pain to the spinal cord and from there to the brain, while autonomic nerves control the calibre of blood vessels, heart rate, gut contraction and other functions not under conscious control.

Blockade of neural transmission in the posterior nerve root fibres interrupts somatic and visceral sensation, while blockade of anterior nerve root fibres prevents efferent motor and autonomic outflow. Generally, autonomic and pain fibres are blocked first and motor fibres the last, although the dorsal roots are generally larger than the anterior roots. It is estimated that CSF volume accounts for 80% variability in peak block height and regression of the sensory and motor block. [(24)]

Indications for Spinal Anaesthesia

Neuraxial block is indicated when the surgical procedure can be accomplished with a sensory level of anaesthesia that does not produce adverse patient outcome.[(25)] Spinal anaesthesia is best reserved for operations below the umbilicus. As a primary anaesthetic, spinal anaesthesia is most useful for lower abdominal, inguinal, urogenital, rectal and lower extremity surgery.

Spinal anaesthesia especially benefits older patients and those with systemic disease such as chronic respiratory disease, hepatic, renal and endocrine disorders such as diabetes as it avoids polypharmacy of general anaesthetics and manipulation of the airway.

Contraindications to Spinal Anaesthesia

Most of the contraindications to spinal anaesthesia apply equally to other forms of regional anaesthesia as well and these include –

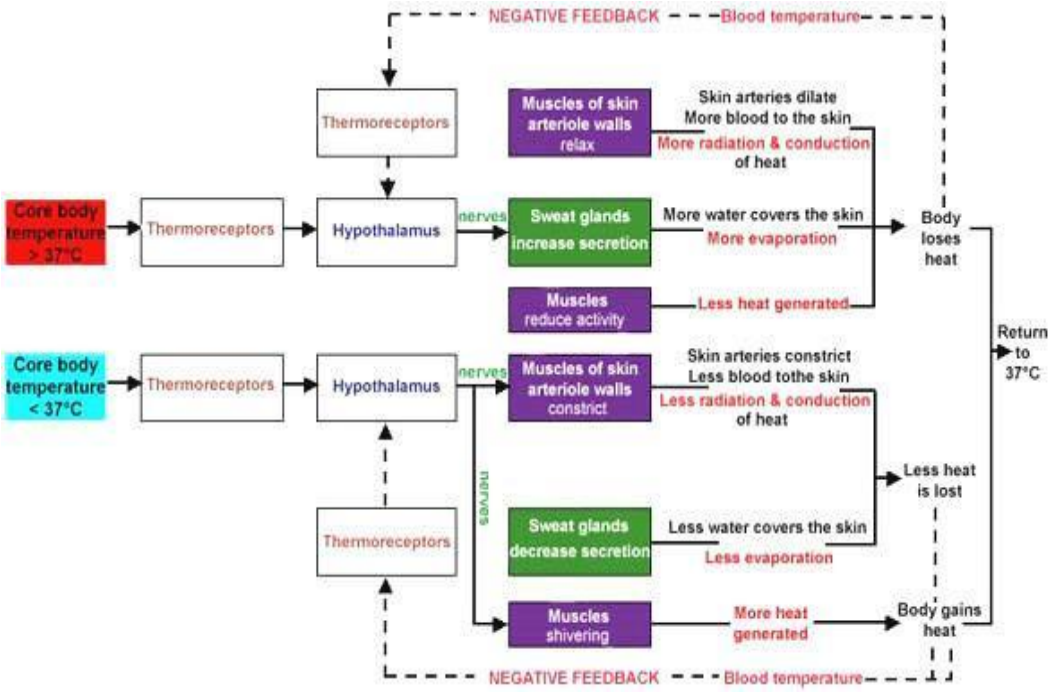
Absolute contraindications

- Patient refusal
- Infection at site of injection
- Severe hypovolemic
- Coagulopathy and other bleeding diathesis
- Severe aortic or mitral valve stenosis
- Increased intracranial pressure

Relative contraindications

- Uncooperative patient/ inability to maintain stillness during procedure
- Pre-existing neurological deficit
- Severe spinal deformity
- Stenotic valvular heart lesions
- Prior back surgery at the site of injection
- Prolonged surgery
- Manoeuvres that compromise respiration

Fig :1 Physiology of thermoregulation and post anaesthetic shivering:



In homeothermic species, a thermoregulatory system coordinates defences against environmental temperature to maintain internal body temperature within a narrow range, thus optimizing normal body function. [27]

Thermoregulation

The processing of thermoregulatory response has three components: afferent thermal sensing, central regulation and efferent responses. Together they work to maintain normal core body temperature. [27,28,29]

Afferent thermal sensing

Signals from cold receptors travel along a delta fibres. These receptors have a peak discharge of impulses at 25 to 30^0c .Signals from warmth receptors are conveyed by C fibres. These receptors have a maximal discharge at 45 to 50^0C. In addition there are central cold receptors which are of uncertain anatomical location. Central cold

thermo reception is considerably less important than peripheral cold sensory reception. Studies in patients with spinal cord transection have suggested that this central thermoregulatory process becomes active when core temperature approaches the lower limit of its set point range and is less sensitive than peripheral thermo receptor.

Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information. Consequently entire anterior cord should be destroyed to ablate thermoregulatory responses. Thermal inputs get integrated at the level of spinal cord, its ability to sense and modulate thermal signals was pivotal for development of currently accepted multiple multilevel concept of thermoregulation. All thermoregulatory effector mechanisms are modulated by spinal cord, eventually it arrives at the hypothalamus, the primary thermoregulatory control centre in mammals.

Two anatomically separate groups of neurons are involved in thermal responsiveness and control the thermoregulatory muscle tone and shivering in the reticular formation of rat. A comparative study in vertebrates also concludes that peripheral thermal input to the hypothalamic areas is via the polysynaptic nonspecific reticular areas in the brain stem. The nucleus raphe magnus and the subcoeruleus area of the brainstem are important relay stations in the transmission of thermal information from skin to hypothalamus. [30,31]

The hypothalamus, other parts of brain, the spinal cord, deep abdominal and thoracic tissues, and the skin surface each contributes roughly to 20%each of the total thermal input to the central regulatory system. [32]

The Nucleus Raphe Magnus and the Subcoeruleus area.

The nucleus raphe magnus in the medulla contains a relatively high percentage of serotonergic thermo responsive neurons, with a preponderance of warm responsive neurons. The locus subcoeruleus is a circumscribed area in the pons ventromedial to the locus coeruleus, which contains the largest cluster of noradrenergic neurons in the brain. The nucleus raphe magnus and the subcoeruleus area appear to be important relay stations in the transmission of thermal information from skin to hypothalamus. These areas seem to be responsible for the modulation rather than the generation of thermal afferent information. [33]

Central regulation

Preoptic region of the anterior hypothalamus is the dominant autonomic thermoregulatory controller in mammals. The anterior hypothalamus conducts the integration of afferent thermal information, whereas the posterior hypothalamus controls the descending pathways to the effectors.

The pre-optic area of hypothalamus contains temperature sensitive and temperature insensitive neurons. The latter respond to non-thermal information such as reproductive hormones, plasma osmolality, glucose concentration, BP (Blood Pressure), noxious stimuli, CO2 and emotional stimuli. The former may be divided into heat sensitive and cold sensitive neurons. The number of heat sensitive neurons is four times the cold sensitive neurons. The heat sensitive neurons increase their discharge rate in response to increased local heat and this activates heat loss mechanism. Cold sensitive neurons, conversely, increase their rate of discharge in response to cooling of pre-optic area of hypothalamus Much of the excitatory input to warm sensitive neurons comes from hippocampus, which links the limbic system (emotion, memory, and behaviour), to thermoregulatory responses. Warm sensitive

neurons in the preoptic anterior hypothalamus along with sensing of core temperature also compare local information with thermal and nonthermal synaptic afferents arriving from ascending pathways. Though integrated by hypothalamus, most of the thermal information is pre-processed in spinal cord and other parts of central nervous system. This hierarchic arrangement presumably developed when evolving thermoregulatory system co-opted previously existing mechanisms like use of postural and locomotry muscles for shivering.[27,33]

In addition, the level of activity in preoptic neurons is modulated by arousal state and suprachiasmatic nucleus activity, which may explain why changes in body temperature are associated with sleep and circadian rhythms. Thus, warm-sensitive neurons in the preoptic anterior hypothalamus not only sense core temperature but also compare local information with thermal and nonthermal synaptic afferents arriving over ascending pathways.[27,33] Classic neuronal models of the hypothalamus functionally separate the integrative and effector neurons controlling thermoregulatory responses.

Electrophysiological studies suggest that some anterior hypothalamic neurons act as “Sensors” as well as “integrators”. These interactions are inevitable because the thermoregulatory system has few specific effector organs, and must be understood as a part of adaptive response of the organism as a whole. [27,33]

The slope of response intensity versus core temperature defines the gain of thermoregulatory response. A response intensity no longer increasing with further deviation in core temperature identifies the maximum intensity. This system of gains and thresholds model is complicated by interactions between other thermoregulatory responses. (i.e. vascular volume control) and time dependent effectors.[34]

Autonomic thermoregulation is dominated by four neural mechanisms:

1. Central detection of warmth
2. Peripheral detection of cold
3. Central warm inhibition of metabolic response to cold
4. Inhibition of thermoregulatory sweating by cooling of skin

The mechanism by which body determines absolute threshold temperature is largely not known, but the mechanism appears to be mediated by norepinephrine, dopamine, 5-hydroxytryptamine, acetylcholine, prostaglandin E1 and neuropeptides. Thresholds vary daily in both sexes (circadian rhythm) and monthly in women by approximately 0.5^0c. Exercise, food intake, infection, hypothyroidism and hyperthyroidism, anaesthetic and other drugs, cold and warm adaptation alter threshold temperatures.[29]

Control of autonomic responses is approximately 80% determined by thermal input from core structures, in contrast, a large fraction of behavioural response is derived from skin surface. The inter threshold range, (core temperature not triggering autonomic thermoregulatory responses) is only 0.4^0C (36.7^0C to 37.1^0C). This threshold is bounded by sweating threshold at its upper end and by vasoconstriction at lower. The inter-threshold range maybe increased to 4.0^0C during general anaesthesia in human volunteers.[29]

Both sweating and vasoconstriction thresholds 0.3^0c-0.5^0c higher in women than men, even during follicular phase of menstrual cycle. Differences are even greater in luteal phase. Central thermoregulatory control is somewhat intact even in premature neonates. In contrast, thermorgulatory control is sometimes impaired in elderly. [29,34]

Efferent responses

Multiple inputs are integrated into a common efferent signal to the effector systems. In both animals and humans, effector mechanisms are called upon in an orderly fashion, ensuring optimal regulation.[16,24] The body responds to thermal perturbations by activating effector mechanisms that increase metabolic heat production or alter environmental heat loss. Each thermoregulatory response has its own threshold and gain, so there is orderly progression of responses and response intensities in proportion to need.[34]

The thermoregulatory responses are characterized by-

1) Altered behaviour, quantitatively the most effective mechanism
2) Vasomotor response, consisting of vasoconstriction and pilo-erection in response to cold, vasodilatation and sweating in response to heat
3) Shivering and increase in metabolic rate. [34]

Activation of thermoregulatory effector responses are triggered at specific temperatures for a given individual (threshold temperature).

In the conscious individual, behaviour modification is more powerful than the autonomic mechanisms in regulating body temperature. When the hypothalamic thermostat indicates an excessively cool body temperature, impulses pass from the hypothalamus to the cerebral cortex to give the individual the sensation of feeling cold. The result is modified behaviour such as increased motor activity, moving to warmer surroundings or adding clothing.

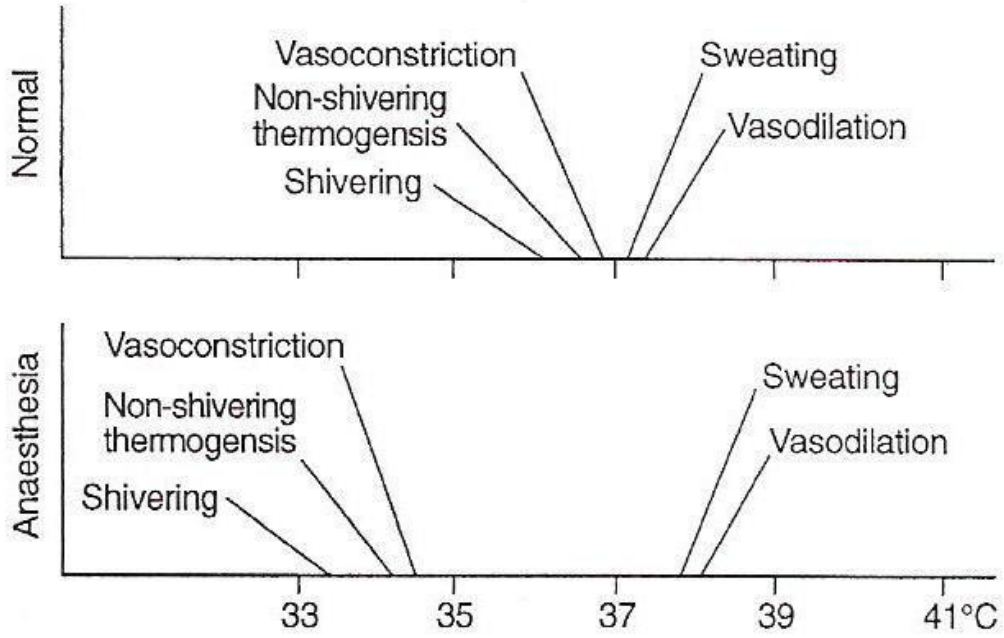


Fig :2 Effect of anaesthesia on temperature and cold effector responses.

Once the set point temperature range 36.7 to 37.10C has been breached, autonomic effector responses are activated. Each of the specific responses has a characteristic threshold (activation at a specific temperature), gain (rate of response increases as deviation from normal increases) and maximum response intensity (response intensity no longer increasing with further deviation from core temperature). Cutaneous vasoconstriction is the most consistently used autonomic effector mechanism. Heat loss is normally regulated without the major responses of sweating or shivering because cutaneous vasodilatation and vasoconstriction usually suffice. Thermoregulatory vasoconstriction decreases cutaneous heat loss and constrains metabolic heat to core thermal compartment. This usually prevents body temperature from decreasing to the required additional 1^0C to activate intraoperative shivering.

Shivering is the last defence that is activated only when behavioural compensation and maximum A-V shunt vasoconstriction are insufficient to maintain core temperature.

Metabolic heat is lost primarily through convection and radiation from the skin surface, vasoconstriction reduces this loss. Total digital blood flow is divided into nutritional (mostly capillary) and thermoregulatory (mostly A-V shunt) vasoconstriction. [34]

The central temperature system has biologic rhythms. Fluctuations in core temperature occur daily with the lowest temperatures occurring in the early hours of morning in relation to melatonin secretion. These circadian rhythms can produce variations of up to 1.5^0C.[34]

Shivering

Shivering is an involuntary, oscillatory muscular activity that augments metabolic heat production. Vigorous shivering increases metabolic heat production up to 600% above basal level. However, a doubling of metabolic heat production is all that can be sustained over long periods. The fundamental tremor frequency on the electromyogram in humans is typically near 200 Hz. This basal frequency is modulated by a slow, 4–8 cycles/ min, waxing-and-waning pattern. [33]

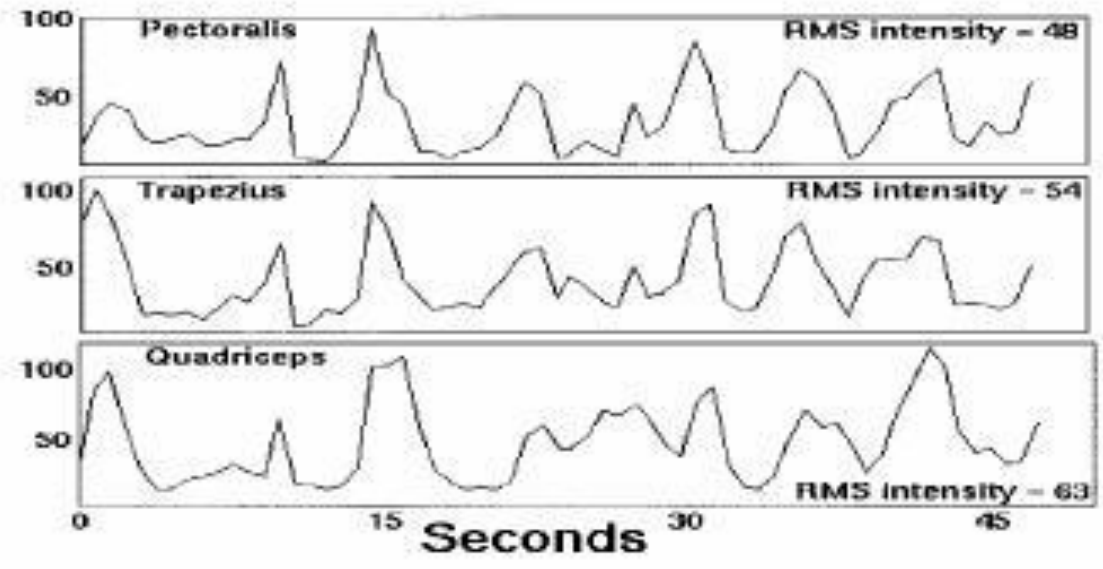
Shivering is elicited when the preoptic region of the hypothalamus is cooled. Efferent signals mediating shivering descend in the medial forebrain bundle. Classically, a central descending shivering pathway was thought to arise from the posterior hypothalamus. Although the preoptic-anterior hypothalamus is thought to suppress shivering by inhibition of the posterior hypothalamus, experimental evidence is lacking. 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. It remains to be determined whether the reticulospinal neurons receive synaptic input directly from the preoptic-anterior hypothalamus or from the posterior hypothalamus. (33)

Spinal 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. One hypothesis suggests that excitability of motor neurons is inversely proportional to cell size.

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. (33)

The larger motor neurons are more likely to manifest synchronized discharges than smaller ones. Synchronization of motor neurons during shivering may be mediated by recurrent inhibition through Renshaw cells, a group of inhibitory interneuron. (27)



Thermoregulation during general anaesthesia

Major disturbances in thermoregulation are observed during and after general anaesthesia. The induction of general anaesthesia impairs the function of neurons in the preoptic nuclei and hypothalamus thus reducing the temperature at which activation of responses to hypothermia usually occurs.

Behavioural adaptations are not relevant in a patient under general anaesthesia who is unconscious and frequently paralysed. All general anaesthetics tested markedly inhibit autonomic thermoregulatory control. Anaesthetic induced thermoregulation slightly elevates the warm response and markedly reduces cold response threshold. The interthreshold range is increased from its normal value of near 0.2^0 to approximately $2\text{-}4^0$c. The gain and maximum intensity of some responses remain normal, whereas others are reduced by general anaesthesia. [35]

Thermoregulation during regional anaesthesia

Epidural and spinal anaesthesia decrease the vasoconstriction and shivering thresholds to a comparable degree (by 0.6^0c), but to a lesser amount than when measured at the level above the upper level of the block. [35]

The gain of shivering response is reduced by 63% and maximum intensity by 33% in regional anaesthesia. This occurs because shivering above block compensates for the inability of muscles below the block to engage in shivering.

As with general anaesthesia core temperature decreases by $0.6\text{-}1.5^0$c during first hour of epidural anaesthesia due to core-to-peripheral distribution of heat due to epidural induced vasodilatation. However, with prolonged epidural anaesthesia the degree of core hypothermia is less than that observed during general anaesthesia. This

is explained by the fact that vasoconstriction above the block compensates for heat losses in epidural anaesthesia. [34]

Shivering during regional anaesthesia is, like that after general anaesthesia is preceded by core hypothermia and vasoconstriction above the level of block. It has the same electromyography characteristics as that of shivering which occurs after general anaesthesia. With reduced gain and maximum intensity, the shivering which is induced by core hypothermia after regional anaesthesia is usually ineffective in preventing core hypothermia. [34]

Interestingly, core hypothermia during regional anaesthesia may not trigger a sensation of cold. This may reflect the fact that subjective cold perception depends on skin temperature afferent input, and that cutaneous vasodilatation resulting from regional anaesthesia increases skin temperature, leading to sensation of warmth although accompanied by thermoregulatory shivering. Awareness of core hypothermia is also impaired by epidural anaesthesia.

After the core to peripheral redistribution of body heat with induction of general and regional anaesthesia, subsequent development of hypothermia depends on balance of cutaneous heat loss and rate of metabolic heat production. [34]

Origins of Post anaesthetic Shivering

Several hypotheses have been raised to explain the occurrence of post anaesthetic shivering. These include perioperative hypothermia, postoperative pain, perioperative heat loss, the direct effect of certain anaesthetics, hypercapnia or respiratory alkalosis, the existence of pyrogens, hypoxia, early recovery of spinal reflex activity and sympathetic over activity.

For slightly more than 10 years, different studies have provided clearer insight into the origins of anaesthesia induced shivering. [36]

One hypothesis used to explain the clonic movements is that they correspond to spinal reflex hyperactivity, which results from the inhibition of descending cortical control by residual concentrations of anaesthetics. These EMG signals are compatible with the clinical descriptions of abnormal reflexes observed during the early recovery phase. [36]

The existence of a link between postoperative pain and the incidence of post anaesthetic shivering has been confirmed by a study comparing the frequency of post anaesthetic shivering after knee arthroscopy in patients who received and those who did not receive intra-articular lidocaine at the end of the operation. The existence of greater pain in patients who did not receive local anaesthesia was accompanied by a higher incidence of post anaesthetic shivering. Most frequently tested and proposed hypothesis of post-operative shivering is anaesthesia induced hypothermia and resulting thermoregulatory shivering. EMG analysis of shivering patterns during anaesthesia and that during hypothermia in normal population are similar. [36]

Of allthe different hypothesis raised to explain the incidence of post anaesthetic shivering, only perioperative hypothermia and pain have been clearly verified. Furthermore, it is indeed a drop in core temperature that facilitates the emergence of shivering and not a reduction in the heat content of the patient. In fact, the initial decrease in central temperature during the inhibition of thermoregulation by anaesthetics is first of all due to an internal redistribution of the heat content, which is carried out with a quasi-zero heat balance. As hypothermia and pain are known to initiate sympathetic over activity, it is difficult to specifically evaluate the influence of Sympathetic over activity on post anaesthetic shivering. [36]

Consequences of Post anaesthetic Shivering

The first clinical consequence of post anaesthetic shivering is discomfort and stressful sensation to the patient. Most patients mention shivering and the sensation of coldness as priorities when queried about the events that should be avoided after an operation. Another consequence of post anaesthetic shivering on the comfort of the patient is the increased pain caused by muscular contractions on the operated site and associated tension on suture lines. After ophthalmological surgery, post anaesthetic shivering increases intra-ocular pressure that can be pernicious shivering also increases intracranial tension. Shivering is perceived as unpleasant experience by the parturient under regional anaesthesia. Shivering can also detract parturient and spouse from the birth, disrupting the family-oriented birth experience sharing. Ostheimer and Datta have noted that of all the side effects associated with anaesthesia and birth such as nausea, vomiting, headache, and bladder catheterization, shivering alone was the only symptom particularly mentioned as a disconcerting and unacceptable part of the birth experience. [36]

The main effect of post anaesthetic shivering is the increase in oxygen consumption (VO2). By affecting several muscular groups for periods of 45 minutes or more, post anaesthetic shivering triggers an increase in metabolic demand, which generally translates into higher VO2 combined with increased minute ventilation. Sometimes, but this is quite rare, metabolic demand can exceed the capacity to deliver oxygen peripherally and result in anaerobic metabolism. [33,34,36]

Prospective randomized data suggest that high risk patients assigned to only 1.3 degree Celsius core hypothermia were three times more likely to experience adverse myocardial outcomes. Marked increase in plasma catecholamine level is perhaps associated with high-risk cardiac complications. Post anaesthetic shivering increases VO2 by approximately 40 to 120%. Mild perioperative hypothermia doubles the incidence of morbid cardiac events among patients who either have coronary artery disease or are at high risk for coronary disease. Hence, strategies to prevent perioperative shivering is necessary for the comfort and safety of the patients.[34]

Measures to combat shivering

Measures which reduce core hypothermia in turn reduce anaesthesia induced shivering. They include:

1. Passive insulators

Cotton blankets, cloth or paper surgical drapes, disposable plastic drapes, plastic bags. Passive insulators reduce heat loss to environment. Heat conservation is proportional to area of body covered. A single layer of each type of covering material decreases heat loss by approximately 30%. A single layer of an insulator reduces the heat loss by approximately 30%; unfortunately adding additional layers does not

proportionately increase the benefit. However this is not beneficial in long and extensive surgeries. [34]

2. Active warming

Active warming systems: Convection warming system where warmed air is forced through a quilt like porous blanket; it passes over the skin warming it directly and also replaces the normal body "air envelope" with a warm air envelop (Bair Hugger Unit).This is the most effective system for conservation of body heat. Radiant heat system infra-red light, thermal ceiling lights can be used for warming body. [34]

Other measures like warming inspired air, warming intravenous fluids, blood and blood components before infusion. Maintaining warm post-operative environment (24^0c), are useful in preserving body temperature and reducing shivering. [34]

3. Pharmacotherapy

Potent ant shivering properties have been attributed to numerous drugs. These drugs are substances of several classes including biogenic monoamines, cholinomimetics, cations, endogenous peptides and possibly N-methyl-D- aspartate (NMDA) receptor antagonists. All these appear to modulate central thermoregulatory control mechanisms. The normal functions of these drugs are diverse and the predominant site of action of most of these drugs is difficult to establish. [27]

PHARMACOLOGY OF DEXMEDETOMIDINE

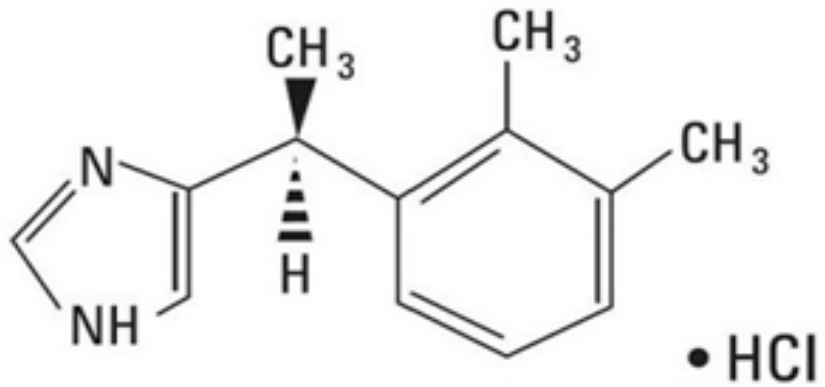


FIG 4: CHEMICAL STRUTCURE OF DEXMEDETOMIDINE

Dexmedetomidine is a new alpha2-agonist that received FDA approval in 1999 for use as a short-term (less than 24 h) sedative-analgesic in the intensive care unit. The use of alpha2-agonists as anaesthetics is not new since many alpha2-agonists are used in veterinary medicine to induce anaesthesia. Clonidine, the prototype of alpha2-agonists, has been synthesized in early 1970's for its use as nasal decongestant and antihypertensive drug. Clonidine is widely used as an adjunct to anaesthesia and pain medicine; however, it has been little used as sedative [(37)].

With dexmedetomidine, there are a number of reasons for the growing and renewed interest in the use of alpha2-adrenoceptors agonists as sedatives: Dexmedetomidine compared to Clonidine is a much more selective alpha2-adrenoceptor agonist, which might permit its application in relatively high doses for sedation and analgesia without the unwanted vascular effects from activation of alpha1-receptors. In addition, Dexmedetomidine is shorter-acting drug than clonidine and has a reversal drug for its sedative effect, Atipamezole. These properties render

Dexmedetomidine suitable for sedation and analgesia during the whole perioperative period: as premedication, as an anaesthetic adjunct for general and regional anaesthesia, and as postoperative sedative and analgesic [38].

Physiology of alpha2-adrenoceptors

Alpha2-receptors are found in many sites throughout the body. Alpha2-adrenoceptors are found in peripheral and central nervous systems, in effector organs such as the liver, kidney, pancreas, eye vascular smooth muscles and platelets. Physiologic responses mediated by alpha2-adrenoceptors vary with location and can account for the diversity of their effects.

The classification of alpha2-receptors based on anatomical location is complicated since these receptors are found in presynaptic, postsynaptic and extrasynaptic locations. Alpha2-adrenoceptors are divided into three subtypes; each subtype is responsible uniquely for some of the actions of alpha2-receptors. The subtype A, the predominant subtype in CNS, is responsible for the sedative, analgesic and sympatholytic effect; the subtype B, found mainly in the peripheral vasculature, is responsible for the short-term hypertensive response, and the subtype C, found in the CNS, is responsible for the anxiolytic effect [39].

There is no alpha2-subtype agonist and therefore the goal of producing a desirable alpha2-agonist effect such as sedation without the unwanted effect such as hypotension is elusive. All the subtypes produce cellular action by signalling through a G-protein which couples to effector mechanisms. This coupling appears to differ depending on the receptor subtype and location. The alpha2 A-adrenoceptor subtype seems to couple in an inhibitory fashion to the calcium channel in the Locus Ceruleus

of the brainstem, whereas, in the vasculature, the alpha2 B-adrenoceptor subtype couple in an excitatory manner to the same effector mechanism [40].

Mechanism of action of Dexmedetomidine

The mechanism of action of dexmedetomidine is unique and differs from the currently used sedative drugs. Alpha2-adrenoceptors are found in many sites through the CNS, however, the highest densities of alpha2-receptors are found in the Locus Ceruleus, the predominant noradrenergic nuclei of the brainstem and an important modulator of vigilance. Presynaptic activation of the alpha2-A adrenoceptor in the Locus Ceruleus inhibits the release of norepinephrine (NE) and results in the sedative and hypnotic effects [9]. In addition, the Locus Ceruleus is the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. Stimulation of the alpha2-adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha2-adrenoceptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia. Also, activation of the alpha2-adrenoceptors in the CNS results in an augmentation of cardiac-vagal activity. Combined, these effects can produce analgesia, sedation and anxiolysis.

At the spinal cord, stimulation of alpha2-receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of the release of substance P [10]. Also, the alpha2-adrenoceptors located at the nerve endings have a possible role in the analgesic mechanisms of alpha2-agonists by preventing NE release. The spinal mechanism is the principal mechanism for the analgesic action of Dexmedetomidine even though there is a clear evidence for both a supraspinal and peripheral sites of action [41].

Alpha2-recepots are located on blood vessels where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit NE release. The responses of activation of alpha2-adrenoceptors in other areas include contraction of vascular and other smooth muscles; decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract, inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased insulin release from the pancreas, decreased intraocular pressure, decreased platelet aggregation and decreased shivering threshold by 2°C [(4)].

Pharmacodynamics of Dexmedetomidine

Alpha-adrenoceptor agonists have different alpha2/alpha1 selectivity. Clonidine, the first developed and the most known alpha2- agonist is considered as a partial alpha2-agonist since its alpha2/alpha1 selectivity = 200, while the alpha2/alpha1 selectivity of dexmedetomidine is 1620 and hence is 8 times more powerful alpha2-adrenoceptor than clonidine and is considered as a full alpha2 adrenoceptor agonist [(5)]. The alpha2-adrenoceptor selectivity of dexmedetomidine is dose-dependent; at low to medium doses or at slow rates of infusion, high levels of alpha2-adrenoceptor selectivity are observed, while high doses or rapid infusions of low doses are associated with both alpha1 and alpha2 activities [(42)].

Dexmedetomidine-induced sedation qualitatively resembles normal sleep. The participation of nonrapid eye movement sleep pathways seems to explain why patients who appear to be “deeply asleep” from dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep [(9)]. This type of sedation is branded “cooperative” or “arousable”, to distinguish it from the sedation induced by

drugs acting on the GABA system, such as midazolam or propofol, which produce a clouding of consciousness. Sedation induced by dexmedetomidine is dose-dependent; however, even low doses might be sufficient to produce sedation. Hall evaluated sedation, analgesia and cognition after infusion of small and moderate doses of dexmedetomidine (0.2 and 0.6 μg/kg/h) in seven healthy volunteers. He found that both doses produced significant sedation, analgesia and reduced performance on psychomotor tests. However, dexmedetomidine may lack amnestic properties: more patients who received dexmedetomidine for postoperative sedation were able to recall their ICU stay when compared to those receiving propofol for sedation [(43)].

Studies conducted on human volunteers to explore the analgesic properties of intravenous dexmedetomidine showed conflicting results. Ebert [(44)] found that increasing concentrations of dexmedetomidine resulted in a dose-dependent sedation and analgesia based on VAS pain score in response to the cold pressor test. Jaakola[(45)] found that a single IV dose used for human tourniquet pain resulted in analgesia with a ceiling effect at the dose of 0.5 μg/kg. Another study comparing the analgesic and mental effects of increasing plasma concentrations of dexmedetomidine and alfentanil concluded that systemic dexmedetomidine lacks analgesic efficacy for heat and electrical pain at doses causing mild to severe sedation [(46)]. However, clinical studies showed that systemic administration of the alpha2-adrenoceptor agonists dexmedetomidine and clonidine produce sedative and opioid-sparing effects in the perioperative setting, providing indirect evidence for some analgesic efficacy[(46,47,48)], although it is difficult in this special setting to distinguish between sedation and analgesia as a cause for this opioid-sparing effect. While the analgesic effect of systemic dexmedetomidine is still debatable, administration of an alpha2-agonist (clonidine) via the intrathecal or epidural route provides analgesic effects in

postoperative pain and in neuropathic pain state without severe sedation [37]. This effect is due to sparing of the supraspinal CNS sites from excessive drug exposure resulting in robust analgesia without heavy sedation.

Alpha2-adrenoceptors do not have an active role in the respiratory centre, therefore, dexmedetomidine throughout a broad range of plasma concentration, has minimal effects on the respiratory system [49]. However, doses of 2 μg/kg given as a bolus resulted in short episodes of apnoea. Also, coadministration of dexmedetomidine with other sedatives, hypnotics or opioids is likely to cause additive effects [50].

Dexmedetomidine does not appear to have direct effects on the heart. In the coronary circulation, dexmedetomidine causes a dose-dependent increase in coronary vascular resistance and oxygen extraction, but the supply/demand ratio is unaltered[51]. A biphasic cardiovascular response has been described after the administration of dexmedetomidine. A bolus of 1 μg/kg results in a transient increase in blood pressure (BP) and a reflex decrease in heart rate (HR), especially in the young healthy patients. This initial response is attributed to the direct effects of alpha2 B-adrenoceptor stimulation of vascular smooth muscle. This response can be attenuated by a slow infusion over 10 min, but even at slower infusion rates, the transient increase in mean BP and the decrease in HR over the first 10 min is shown. This initial response lasts for 5 to 10 min and is followed by a decrease in BP of 10-20% below baseline and by stabilization of the HR below baseline values. Both these effects are presumably caused by an inhibition of central sympathetic outflow that overrides the direct effects of dexmedetomidine on the vasculature. Hypotension and bradycardia induced by dexmedetomidine are reversed by ephedrine and atropine respectively, but large doses are required [52].

Ebert[44] studied the autonomic, cardiovascular, and sedative responses to increasing plasma concentrations of dexmedetomidine; he found that low plasma concentrations resulted in sedation, mild analgesia with preservation of recall and recognition. In addition, it resulted in a decrease in HR and BP, without changes in central venous pressure or pulmonary artery pressure and without respiratory changes. Subsequent higher doses resulted in increased sedation, analgesia and memory impairment, as well as an increase in BP, systemic and pulmonary vascular resistance. A significant decrease in HR and progressive decreases in cardiac output, and stroke volume is also noted. Even at higher doses, there was no respiratory compromise.

Pharmacokinetics of Dexmedetomidine

Dexmedetomidine, an imidazole compound, is the active d-isomer of medetomidine. Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{½\ \alpha}$) of 6 min, a terminal elimination half-life ($t_{½\ \beta}$) of 2 hours, and a steady-state volume of distribution (Vss) of 118 liters. Dexmedetomidine exhibits linear kinetics when infused in the dose range of 0.2-0.7 μg/kg/h for no more than 24 hours. Dexmedetomidine undergoes almost complete biotransformation through direct glucuronidation and cytochrome P450 metabolism. Metabolites of biotransformation are excreted in the urine (95%) and faeces. It is unknown if they possess intrinsic activity.

The average protein binding of dexmedetomidine is 94%, with negligible protein binding displacement by fentanyl, digoxin, theophylline, lidocaine and ketorolac. There have been no sex or age-based differences in the pharmacokinetics of dexmedetomidine; however, it has not been studied in paediatric patients. The dose of

dexmedetomidine should be decreased in patients with hepatic or renal impairment. Dexmedetomidine do cross the placenta and should be only used during pregnancy if the potential benefits justify the potential risk to fetus.

Dexmedetomidine is a white powder that is freely soluble in water and has a pka of 7.1. It is supplied as 100 μg/ml 2 ml vial which must be diluted with 48 ml of 0.9% sodium chloride prior to administration. For adult patient, dexmedetomidine is administered by a loading infusion of 0.5-1 μg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 μg/kg/h. The effect appears in 5-10 min, and is reduced in 30-60 min. The maintenance infusion is adjusted to achieve the desired level of sedation [(53)].

The most frequently observed adverse events in patients receiving dexmedetomidine for ICU sedation include hypotension, hypertension, nausea, bradycardia, atrial fibrillation and hypoxia. Most of these events occur after or during the loading dose, therefore, reducing or omitting the loading dose could result in decreasing the incidence and severity of these adverse events [(54)].

Appropriate patient selection for dexmedetomidine administration is crucial; because it decreases sympathetic nervous activity, its effects may be most pronounced in patients with decreased autonomic nervous system control such as the elderly, diabetic patients, patients with chronic hypertension or severe cardiac disease such as valve stenosis or regurgitation, advanced heart block, sever coronary artery disease, or in patients who are already hypotensive and/or hypovolemic [(38)].

The tolerability of dexmedetomidine was noted in three cases of over dosage[(55)]; In 2 cases, the dose administered was 0.5 mg/kg/h instead of 0.5 μg/kg/h, and in one case, the dose 4 μg/kg/h instead of 0.4 μg/kg/h. In the three cases, the over

dosage resulted in oversedation only. However, first and second-degree heart block or even cardiac arrest following administration of dexmedetomidine were reported [56].

Dexmedetomidine do not affect the synthesis, storage or metabolism of neurotransmitters and do not block the receptors, thus providing the possibility of reversing the hemodynamic effects with vasoactive drugs or the specific alpha2-antagonist: Atipamezol (Antisedan) [57]. Atipamezol acts by increasing the central turnover of norepinephrine. Its duration of action is 2 hours [58].

Perioperative uses of dexmedetomidine

I – Premedication

Dexmedetomidine possesses anxiolytic, sedative, analgesic, antisialogogue and sympatholytic properties, which render it suitable as a premedication agent. Dexmedetomidine potentiates the anaesthetic effects of all intraoperative anaesthetics [59,60,61] (intravenous, volatile or regional block). Bohrer [62] showed that preoperative administration of intravenous or intramuscular dexmedetomidine resulted in a decrease in induction dose of thiopentone by up to 30%. The administration of intramuscular dexmedetomidine at a dose of 1 μg/kg for premedication in outpatient cataract surgery resulted in sedation, and decrease in intraocular pressure without significant hypotension or bradycardia [62,63]. Also, the administration of dexmedetomidine for premedication decreases oxygen consumption intraoperatively by 8% and postoperatively by 17%. Indications to the use of dexmedetomidine as premedication include patients susceptible to preoperative and perioperative stress, drug addicts and alcoholics, chronic opioid users and hypertensive patients.

II – Intraoperative uses of dexmedetomidine

Intraoperative uses of dexmedetomidine include its use as adjunct to general anaesthesia, as adjunct to regional anaesthesia, in monitored anaesthesia care (MAC), or as a sole agent for total intravenous anaesthesia (TIVA).

1 – Use of dexmedetomidine as adjunct to general anaesthesia

The use intraoperative dexmedetomidine may increase hemodynamic stability because of attenuation of the stress-induced sympathoadrenal responses to intubation, during surgery and during emergence from anaesthesia [(64)]. Talke[(65)] evaluated the effects of varying plasma concentrations of dexmedetomidine on HR, BP and catecholamines concentrations during emergence from anaesthesia in the setting of vascular surgery. This study demonstrated that dexmedetomidine attenuates the increases in heart rate and plasma norepinephrine levels observed during the emergence from anaesthesia.

Administration of intravenous dexmedetomidine produces an anaesthetic-sparing effect[(65)]. Aho[(66)] showed 25% reduction of maintenance concentrations of isoflurane in patients undergoing hysterectomy. Khan found 35%-50% reduction in isoflurane concentrations with either low or high doses of dexmedetomidine. Fragen[(67)] noted 17% reduction in sevoflurane requirements for maintenance of anaesthesia in elderly patients. In addition, the use of dexmedetomidine produces intraoperative and postoperative opioid-sparing effect. Aho[(49)] administered dexmedetomidine at dose of 0.4 μg/kg in patients undergoing laparoscopic tubal ligation and found a 33% decrease in morphine use postoperatively.

Talke[68] investigated the muscle relaxant effects of dexmedetomidine on the neuromuscular junction and found no clinically relevant effects. Dexmedetomidine reduces the vasoconstriction threshold and the shivering threshold and is associated with a lower incidence of shivering [38].

2 – Use of dexmedetomidine for regional anaesthesia

The use of dexmedetomidine as adjuvant in regional anaesthesia is still not validated. Maarouf [69] explored the effect of epidural dexmedetomidine on the incidence of postoperative shivering in 60 patients undergoing orthopaedic surgery. He found that patients who received dexmedetomidine at a dose of 100 μg added to 20 ml 0.5% bupivacaine showed lower incidence in postoperative shivering when compared to patients who received epidural bupivacaine alone (10% vs. 36%). Memis[70] noted that the addition of 0.5 μg/kg dexmedetomidine to lidocaine for intravenous regional anaesthesia improves the quality of anaesthesia and perioperative analgesia without causing side effects. Kanazi et al[71] investigated the effect of adding a small dose of 3 μg of intrathecal dexmedetomidine to 12 mg bupivacaine. They found a significant prolongation of sensory and motor block as compared to bupivacaine alone. In this study, the effect of 3 μg intrathecal dexmedetomidine was similar to that produced by the addition of 30 μg of intrathecal clonidine.

3 – Use of dexmedetomidine in monitored anaesthesia care

Dexmedetomidine confers arousable sedation with ease of orientation, anxiolysis, mild analgesia, lack of respiratory depression and hemodynamic stability at moderate doses. These properties allow dexmedetomidine to be an almost ideal agent for MAC despite its lack of amnesia and poor controllability because of its slow onset and offset. The efficacy, side effects, and recovery characteristics of

dexmedetomidine were compared to propofol when used for MAC [46]. This study showed that dexmedetomidine achieved similar levels of sedation to propofol, albeit with a slower onset and offset of sedation. Neither dexmedetomidine nor propofol influenced respiratory rate, but propofol resulted in lower mean arterial pressure during the intraoperative period. In the recovery room, dexmedetomidine was associated with an analgesia-sparing effect, slightly increased sedation, but no compromise of respiratory function or psychomotor responses. Dexmedetomidine in MAC was used successfully in many situations: when patient arousability needed to be preserved, as for awake craniotomy [71,72], for awake carotid endarterectomy [73] and for vitreoretinal surgey [74]. In addition, dexmedetomidine was used for sedation in difficult airway patients; during fiberoptic intubation [75,76], and for sedation of a patient with difficult airway undergoing lumbar laminectomy surgery in the prone-chest position under spinal anaesthesia[77].

4 – Use of dexmedetomidine as a sole anaesthetic agent

Ramsay [78] has used dexmedetomidine as a sole anaesthetic agent. The report describes three patients who presented for surgery with potential airway management challenges. Dexmedetomidine was infused in increasing doses (up to 10 μg/kg/h) until general anaesthesia was attained. No respiratory depression was noted, only one patient required chin lift. Also no hypotension or severe bradycardia was noted. The rationale for this new, off-label use of dexmedetomidine is based on its known properties to provide sedation, analgesia while avoiding respiratory depression at low doses. These effects were maintained at higher doses without hemodynamic instability.

III – Use of dexmedetomidine in the postoperative period

Dexmedetomidine special properties favour its use in recovery room. In addition to its sympatholytic effects, analgesic effects and decreased rate of shivering, the preservation of respiratory function allows the continuation of the dexmedetomidine infusion in the extubated, spontaneously breathing patient. The possibility of ongoing sedation and sympathetic block could be beneficial in reducing high rates of early postoperative ischemic events in high-risk patients undergoing non-cardiac surgery[79]. In a study conducted by Talke [66], high-risk patients who received dexmedetomidine from 1 h before until 48 h after vascular surgery experienced significantly fewer ischemic episodes than did patients in the placebo group (8% vs 29%). During emergence from anaesthesia, NE levels in the placebo group were 2 to 3 times higher than those in the dexmedetomidine group. However, patients who received intraoperative dexmedetomidine needed more fluids to avoid hypotension, a side effect that may be unfavourable in volume-sensitive patients with reduced left ventricular function. In addition, care should be taken in patients who depend on a high level of sympathetic tone or in patients with reduced myocardial function who cannot tolerate the decrease in sympathetic tone [38]. Perioperative administration of dexmedetomidine could be beneficial in chronic opioid users and alcoholics, in high-risk patients as well as in cardiac patients with good to moderately decreased left ventricular function.

IV – Use of Dexmedetomidine in the paediatric-age group

Only few cases about the use of dexmedetomidine in the paediatric-age group are found in the literature[78,80]. Tobias used dexmedetomidine for ICU sedation in 10-week old infant requiring mechanical ventilation and in a 14-y old patient after posterior spinal fusion for scoliosis. The use of dexmedetomidine at a dose of 0.25

μg/kg/h for 24 h in these two cases resulted in acceptable sedation without significant hemodynamic changes. Dexmedetomidine was also used for sedation and anaesthesia in an 11-y old patient undergoing gastroscopy; however, it resulted in insufficient sedation. Another study conducted in paediatric-age group explored the use of intraoperative dexmedetomidine at different doses with the goal of reducing the post sevoflurane agitation in children aged 1-10 y. The optimal dose of dexmedetomidine was 0.3μg/kg and its use did not result in adverse effects [81].

PHARMACOLOGY OF PETHIDINE

Pethidine is predominantly a μ-opiod receptor (MOR) agonist that produces a pattern of effects similar but not identical to those of morphine.

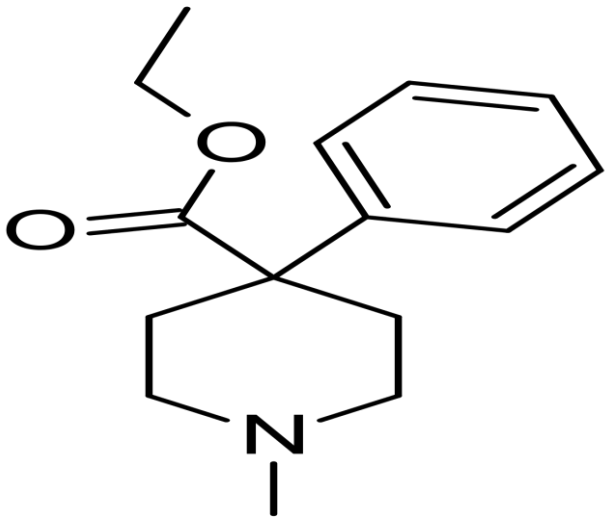


FIG 5: Chemical structure of Pethidine

Effects on Organ Systems

CNS Actions

Pethidine is a potent MOR agonist yielding strong analgesic actions. Peak respiratory depression is observed within 1 hour of intramuscular administration, and there is a return toward normal starting at ~2 hours [82]

Like other opioids, pethidine causes pupillary constriction, increases the sensitivity of the labyrinthine apparatus, and has effects on the secretion of pituitary hormones similar to those of morphine. Pethidine sometimes causes CNS excitation, characterized by tremors, muscle twitches, and seizures; these effects are due largely to accumulation of a metabolite, norpethidine.

Pethidine has well-known local anaesthetic properties, particularly noted after epidural administration. As with morphine, respiratory depression is responsible for

an accumulation of CO2, which in turn leads to cerebrovascular dilation, increased cerebral blood flow, and elevation of cerebrospinal fluid pressure [82].

Cardiovascular System

The effects of pethidine on the cardiovascular system generally resemble those of morphine, including the ability to release histamine following parenteral administration.

Intramuscular administration of pethidine does not affect heart rate significantly, but intravenous administration frequently produces a marked increase in heart rate [82].

Smooth Muscle

Pethidine has effects on certain smooth muscles qualitatively similar to those observed with other opioids. Pethidine does not cause as much constipation as does morphine, even when given over prolonged periods of time; this may be related to its greater ability to enter the CNS, thereby producing analgesia at lower systemic concentrations. As with other opioids, clinical doses of pethidine slow gastric emptying sufficiently to delay absorption of other drugs significantly. The uterus of a nonpregnant woman usually is mildly stimulated by pethidine. Administered before an oxytocic, pethidine does not exert any antagonistic effect. Therapeutic doses given during active labor do not delay the birth process; in fact, the frequency, duration, and amplitude of uterine contraction sometimes may be increased (Zimmer et al., 1988). The drug does not interfere with normal postpartum contraction or involution of the uterus, and it does not increase the incidence of postpartum haemorrhage [82].

Absorption, Distribution, Metabolism, and Excretion

Pethidine is absorbed by all routes of administration, but the rate of absorption may be erratic after intramuscular injection. The peak plasma concentration usually occurs at ~45 minutes, but the range is wide. After oral administration, only ~50% of the drug escapes first-pass metabolism to enter the circulation, and peak concentrations in plasma usually are observed in 1-2 hours [82].

In humans, pethidine is hydrolyzed to meperidinic acid, which in turn is partially conjugated. Pethidine also is N-demethylated to norpethidine, which then may be hydrolyzed to normeperidinic acid and subsequently conjugated. Pethidine is metabolized chiefly in the liver, with a t1/2 ≈3 hours. In patients with cirrhosis, the bioavailability of pethidine is increased to as much as 80%, and the t1/2 of both pethidine and norpethidine are prolonged. Approximately 60% of pethidine in plasma is protein bound. Only a small amount of pethidine is excreted unchanged [82].

Untoward Effects, Precautions, and Contraindications.

The pattern and overall incidence of untoward effects that follow the use of pethidine are similar to those observed after equi analgesic doses of morphine, except that constipation and urinary retention may be less common. Patients who experience nausea and vomiting with morphine may not do so with pethidine; the converse also may be true. As with other opioids, tolerance develops to some of these effects. The contraindications generally are the same as for other opioids. In patients or addicts who are tolerant to the depressant effects of pethidine, large doses repeated at short intervals may produce an excitatory syndrome including hallucinations, tremors, muscle twitches, dilated pupils, hyperactive reflexes, and convulsions. These excitatory symptoms are due to the accumulation of norpethidine, which has a t1/2 of 15-20 hours, compared to 3 hours for pethidine [82].

Since norpethidine is eliminated by the kidney and the liver, decreased renal or hepatic function increases the likelihood of toxicity. As a result of these properties, pethidine is not recommended for the treatment of chronic pain because of concerns over metabolite toxicity. It should not be used for longer than 48 hours or in doses >600 mg/day [82].

Interactions with Other Drugs

Severe reactions may follow the administration of pethidine to patients being treated with MAO inhibitors. Two basic types of interactions can be observed. The most prominent is an excitatory reaction ("serotonin syndrome") with delirium, hyperthermia, headache, hyper or hypotension, rigidity, convulsions, coma, and death. This reaction may be due to the ability of pethidine to block neuronal reuptake of 5-HT, resulting in serotonergic over activity (Stack et al., 1988). Conversely, the MAO inhibitor interaction with meperidine may resemble acute narcotic overdose owing to the inhibition of hepatic CYPs. Therefore, pethidine and its congeners are contraindicated in patients taking MAO inhibitors or within 14 days after discontinuation of an MAO inhibitor. Similarly, dextromethorphan (an analogue of levorphanol used as a non-narcotic cough suppressant) also inhibits neuronal 5- HT uptake and must be avoided in these patients. In addition, tramadol and tapentadol inhibit the uptake of norepinephrine and 5-HT and should not be used concomitantly with MAO inhibitors or selective serotonin reuptake inhibitors (SSRIs) [82].

Chlorpromazine increases the respiratory-depressant effects of pethidine, as do tricyclic antidepressants; this is not true of diazepam. Concurrent administration of drugs such as promethazine or chlorpromazine also may greatly enhance pethidine-induced sedation without slowing clearance of the drug. Treatment with phenobarbital

or phenytoin increases systemic clearance and decreases oral bioavailability of pethidine; this is associated with an elevation of the concentration of norpethidine in plasma (Edwards et al., 1982). As with morphine, concomitant administration of amphetamine has been reported to enhance the analgesic effects of pethidine and its congeners while counteracting sedation [82].

Therapeutic Uses

The major use of pethidine is for analgesia. Unlike morphine and its congeners, pethidine is not used for the treatment of cough or diarrhoea. The analgesic effects of pethidine are detectable ~15 minutes after oral administration, peak in 1-2 hours, and subside gradually. The onset of analgesic effect is faster (within 10 minutes) after subcutaneous or intramuscular administration, and the effect reaches a peak in ~1 hour, corresponding closely to peak concentrations in plasma. In clinical use, the duration of effective analgesia is ~1.5-3 hours. In general, 75-100 mg pethidine hydrochloride (pethidine, DEMEROL, others) given parenterally is approximately equivalent to 10 mg morphine, and in equianalgesic doses, pethidine produces as much sedation, respiratory depression, and euphoria as does morphine. In terms of total analgesic effect, pethidine is about one-third as effective when given orally as when administered parenterally. A few patients may experience dysphoria. Single doses of pethidine also appear to be effective in the treatment of post anaesthetic shivering. Pethidine, 25-50 mg, is used frequently with antihistamines, corticosteroids, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent or ameliorate infusion-related rigors and shaking chills that accompany the intravenous administration of agents such as amphotericin B, aldesleukin (interleukin2), trastuzumab, and alemtuzumab. Pethidine crosses the placental barrier and even in reasonable analgesic doses causes a significant increase in the percentage

of babies who show delayed respiration, decreased respiratory minute volume, or decreased O2 saturation or who require resuscitation [82].

Fetal and maternal respiratory depression induced by pethidine can be treated with naloxone. The fraction of drug that is bound to protein is lower in the foetus; concentrations of free drug thus may be considerably higher than in the mother. Nevertheless, pethidine produces less respiratory depression in the new born than does an equianalgesic dose of morphine or methadone [82].

MATERIALS AND METHODS

Research Plan

Source of Data (Sample)

This study was carried out in the Department of Anaesthesiology, B.L.D.E (Deemed to be University) Shri. B. M. Patil Medical College, Hospital and Research Centre, Vijayapura, on those patients who developed intra-operative shivering following spinal anaesthesia for various surgical procedures were included in the study.

Design of study:

Prospective randomized clinical trial

INCLUSION CRITERIA

- Patients of either gender aged between 20-60 years
- ASA grade of I -II
- Patients who develop shivering following spinal anaesthesia
- Shivering of grade 2-3 (Crossley and Mahajan scale)

EXCLUSION CRITERIA

- Patients not belonging to above mentioned age, weight or ASA grade.
- Patients suffering with fevers, drug allergy, thyroid disease and neuromuscular diseases.
- Surgeries lasting more than 4hours.
- Patients who develop shivering even before administering spinal anaesthesia.
- Patients requiring supplementation with general anaesthesia.

Materials and Methods of collection of Data

A prospective, randomized comparative study was conducted after a written informed consent from the patients. Based on the article published by Lin Fern Et al[7], With anticipated mean difference of time elapsed from treatment to cessation of shivering between two study groups as 3.1 and anticipated Standard deviation as 3.8 the minimum sample size per group is 40 with 90% power and 5% level of significance. All patients who were included in the study were pre-medicated with tablet Diazepam 10mg on the night before the surgery and tablet Diazepam 5mg on the morning of the surgery, administered orally with sips of water two hours prior to the planned surgery. They were preloaded with 500ml of Ringers Lactate solution. Patients were shifted to operation theatre and baseline parameters were recorded using monitors. Baseline temperature was recorded using a mercury thermometer in the axilla placed in the vicinity of the axillary artery. Operation theatre temperature was maintained at 22-25C. All patients in our study received spinal anaesthesia in left lateral position using 25G Quinke needles via midline approach in the L3-L4 intervertebral space under strict aseptic precautions and local anaesthesia to the skin. Following free flow of CSF, 0.5% Bupivacaine (hyperbaric) was injected depending on the requirement of surgery (3-4ml). Patients were administered 5 litres of oxygen by Hudson transparent face mask and were adequately covered with surgical drapes. Patients who developed shivering after administering spinal anaesthesia were included in the study. Shivering of grades 2 and 3 as proposed by Crossley and Mahajan Scale of Shivering was considered to require treatment. When patients developed shivering of above mentioned grades, they were randomly allotted to one of the two study groups -

Group D- Dexmedetomidine group receiving single intravenous bolus dose of 0.5mcg/kg over 5 min.

Group P –Pethidine group patients receiving 0.5mg/kg Pethidine IV over 5 min.

The study drug was then administered i.v as per the allotted group. The time from drug administration till the disappearance of shivering was accurately noted in seconds. Patients were monitored at intervals of 1 minute, 3min, 5min and thereafter 10, 20 and 30 minutes till end of surgery. Patients were closely monitored for failure of the drug, recurrence of shivering and side effects such as nausea, vomiting, bradycardia (< 50/min), hypotension(>20% of baseline), dizziness and sedation score will be recorded.

Sedation score was assessed with a four point scale as per Filos

1. Awake and alert
2. Drowsy, response to verbal stimuli
3. Drowsy, arousable to physical stimuli
4. Unarousable

Bradycardia, hypotension and vomiting was treated with Atropine, Mephentermine and Metoclopramide, respectively, in titrated doses when required.

Parameters to be studied

- Grade of shivering: Crossely and Mahajan Scale will be used.

  Grade 0 -No Shivering

  Grade1-Piloerection, peripheral vasoconstriction, peripheral cyanosis without other cause but without visible muscular activity

  Grade 2-Visible muscular activity confined to one muscle group

Grade 3-Visible muscular activity more than one muscle group

Grade 4-Gross muscular activity involving the entire body

- Temperature at onset of shivering
- Time from drug administration to control of shivering
- Disappearance of shivering Yes/No
- Recurrence of shivering after drug administration
- Hemodynamic changes
- Adverse effects of drugs

Statistical analysis

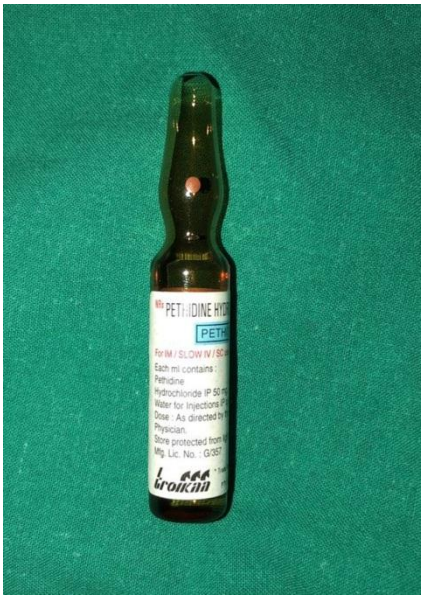
Data was analyzed using Mean+/-Standard deviation, Chi square test for association, comparison of means using T test, Anova for comparison between and within groups and diagrammatic presentation.

SAMPLE SIZE

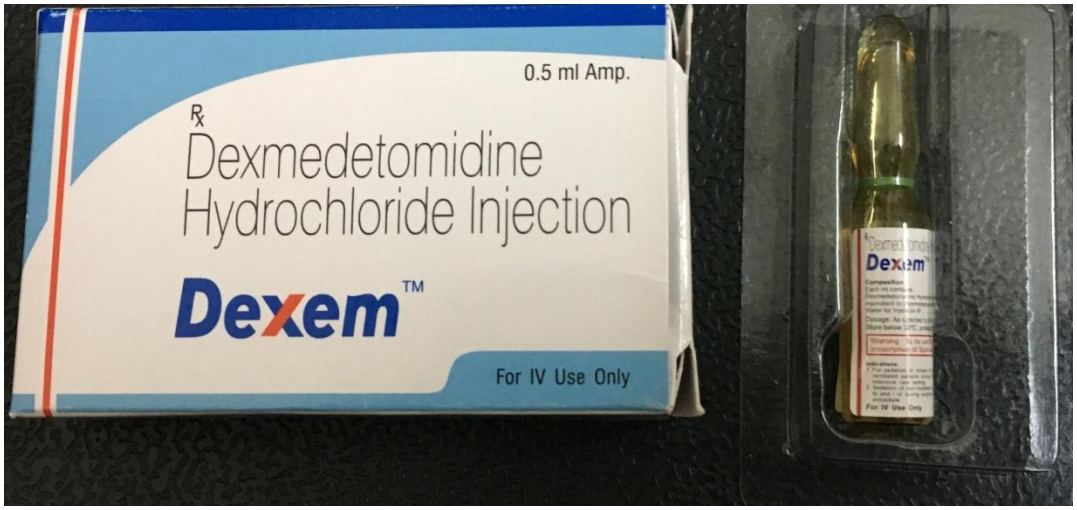
Based on the article published by Lin Fern Et al [7], With anticipated mean difference of time elapsed from treatment to cessation of shivering between two study groups as 3.1 and anticipated Standard deviation as 3.8 the minimum sample size per group is 40 with 90% power and 5% level of significance.

DRUGS USED

1. Pethidine



2. Dexmedetomidine



OBSERVATION AND RESULTS

TABLE: DISTRIBUTION OF GENDER BETWEEN STUDY GROUPS

GENDER	Pethidine		Dexmedetomidine		p value
	N	%	N	%	
Male	25	62.5	21	52.5	0.366
Female	15	37.5	19	47.5	
Total	40	100	40	100	

The gender distribution was comparable with no statistical difference between two groups.

FIGURE: DISTRIBUTION OF GENDER BETWEEN STUDY GROUPS

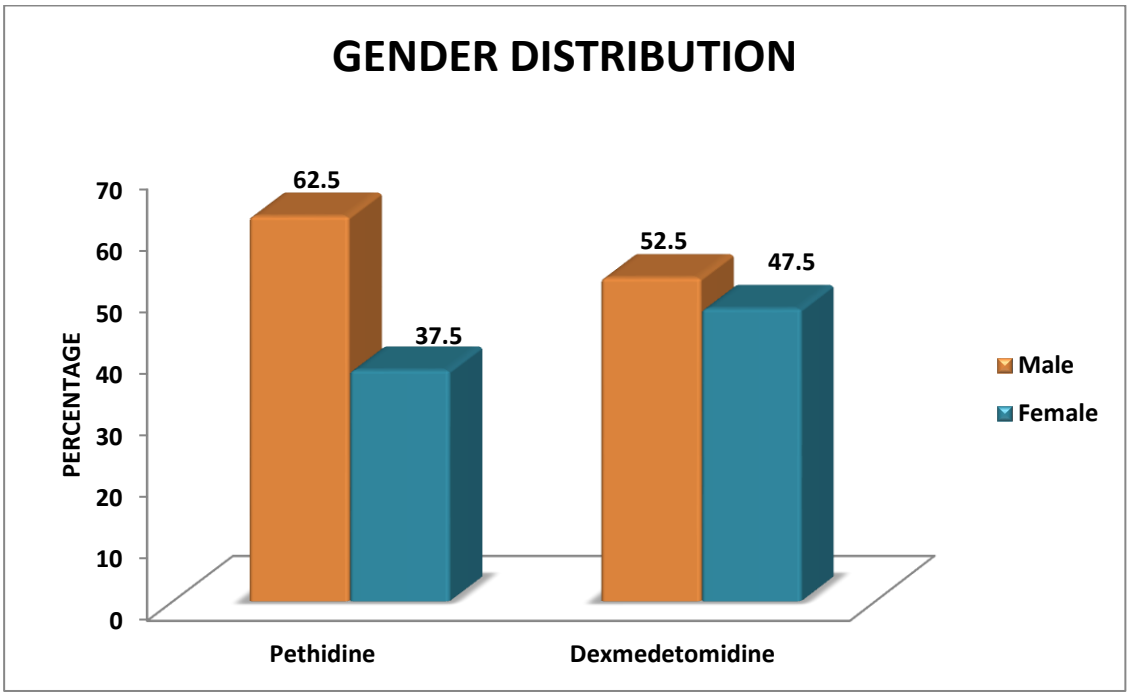


TABLE: MEAN AGE AND WEIGHT BETWEEN STUDY GROUPS

PARAMETERS	Pethidine		Dexmedetomidine		p value
	Mean	SD	Mean	SD	
AGE (YRS)	39.6	11.7	40.5	10.6	0.698
WEIGHT (Kg)	55.3	7.3	57.3	6.8	0.215

FIGURE: MEAN AGE BETWEEN STUDY GROUPS

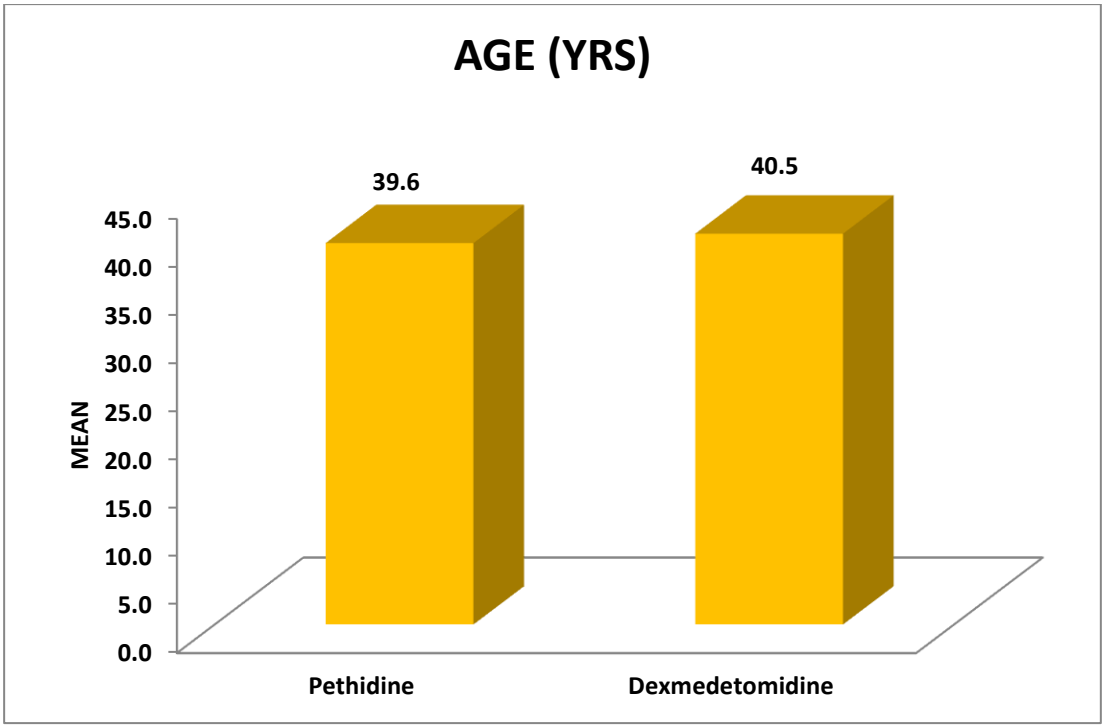
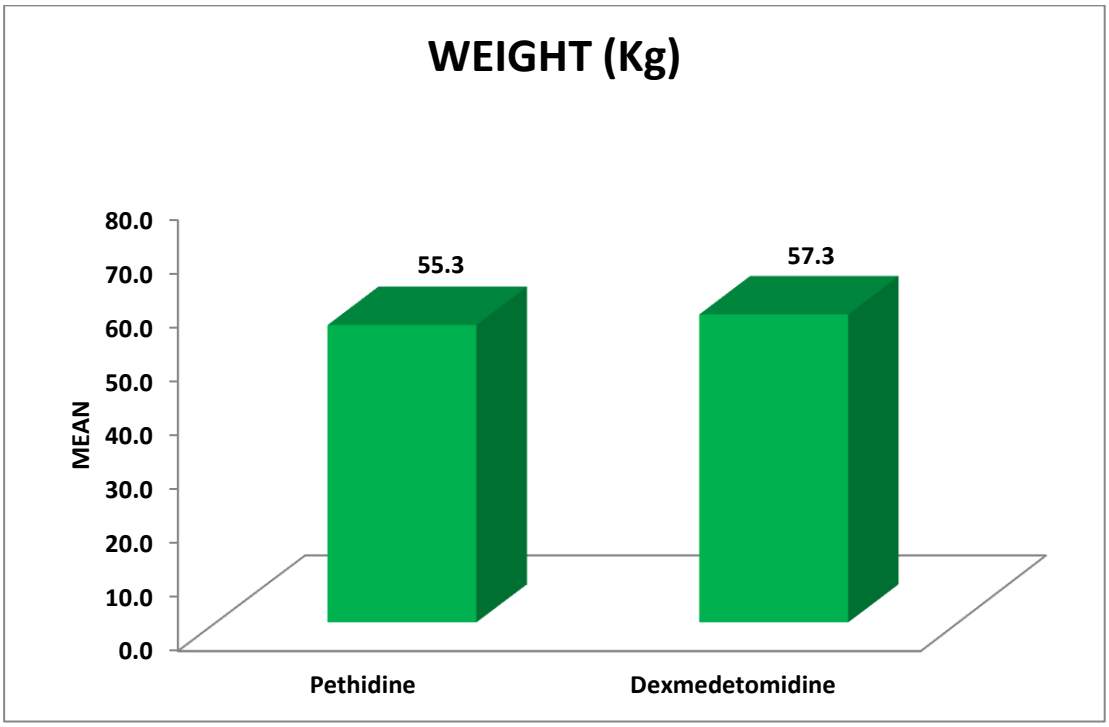


FIGURE: MEAN WEIGHT BETWEEN STUDY GROUPS



The age and weight distribution was comparable with no statistical difference between two groups.

TABLE: DISTRIBUTION OF GRADE OF SHIVERING STUDY GROUPS

GRADE OF SHIVERING	Pethidine		Dexmedetomidine		p value
	N	%	N	%	
1	0	0	0	0	0.693
2	15	37.5	13	32.5	
3	25	62.5	27	67.5	
Total	40	100	40	100	

The grades of shivering was comparable with no statistical difference between two groups.

FIGURE: DISTRIBUTION OF GRADE OF SHIVERING STUDY GROUPS

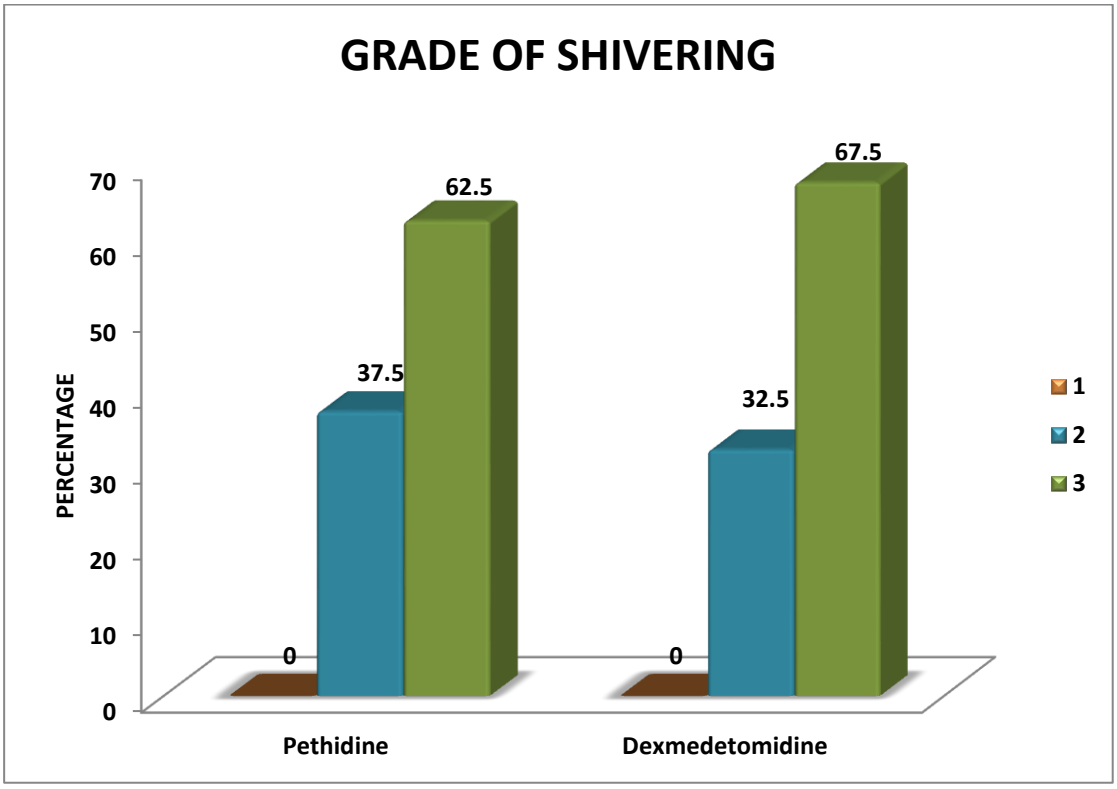


TABLE: MEAN TEMPERATURE BETWEEN STUDY GROUPS

TEMPERATURE	Pethidine		Dexmedetomidine		p value
	Mean	SD	Mean	SD	
PREOPERATIVELY	37.2	0.4	37.2	0.5	0.917
DURING SHIVERING	36.4	0.4	36.4	0.5	0.959

The temperature prior to spinal anaesthesia, temperature during shivering was comparable with no statistical difference between two groups.

FIGURE: MEAN TEMPERATURE BETWEEN STUDY GROUPS

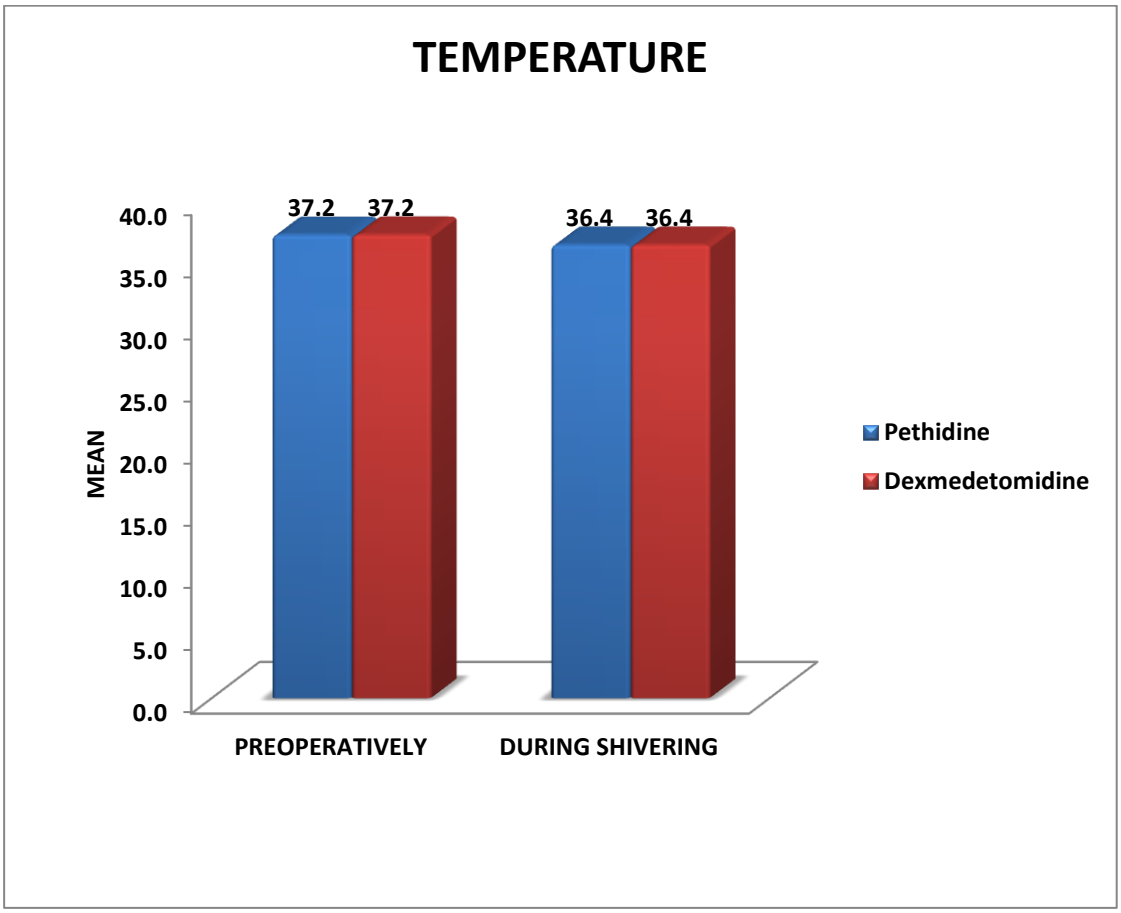


TABLE: MEAN DURATION BETWEEN STUDY GROUPS

DURATION	Pethidine		Dexmedetomidine		p value
	Mean	SD	Mean	SD	
TIME REQUIRED TO CONTROL SHIVERING AFTER DRUG(sec)	413.0	16.8	205.3	18.1	<0.001*
DISAPPEARANCE OF SHIVERING(sec)	515.1	9.9	295.6	8.6	<0.001*

Note: * significant at 5% level of significance (p<0.05)

The time for control and disappearance of shivering was comparable with (p values of <0.001) no statistical difference between two groups.

FIGURE: MEAN DURATION BETWEEN STUDY GROUPS

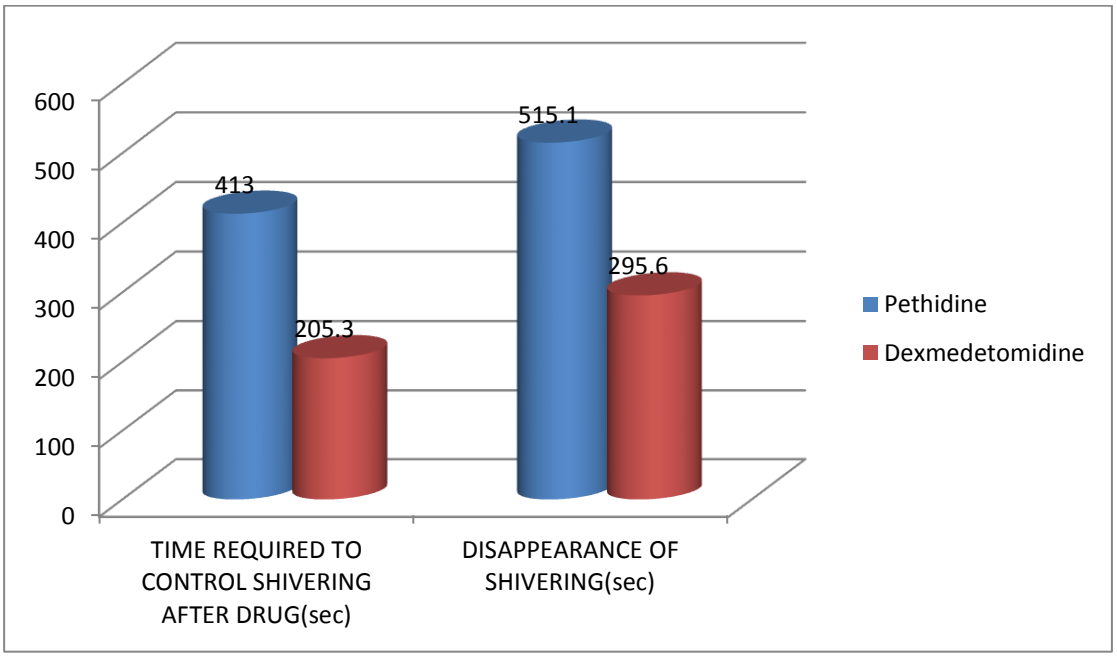


TABLE: MEAN HR BETWEEN STUDY GROUPS

HR	Pethidine		Dexmedetomidine		p value
	Mean	SD	Mean	SD	
DURING SHIVERING	85.1	14.4	79.5	5.8	0.024*
AFTER CONTROL OF SHIVERING	83.5	7.0	72.4	6.1	<0.001*

Note: * significant at 5% level of significance (p<0.05)

The mean heart rate after the control of shivering was statistically significant between the two groups

FIGURE: MEAN HR BETWEEN STUDY GROUPS

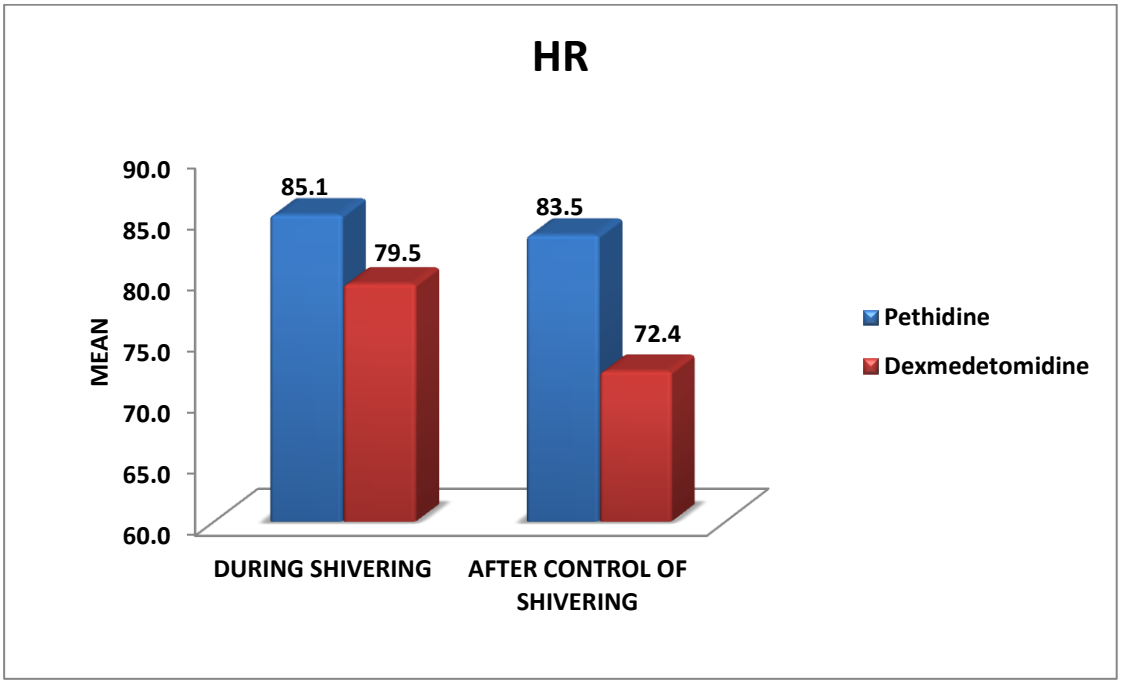


TABLE: MEAN SBP BETWEEN STUDY GROUPS

SBP	Pethidine		Dexmedetomidine		p value
	Mean	SD	Mean	SD	
DURING SHIVERING	110.5	3.0	104.9	4.1	<0.001*
AFTER CONTROL OF SHIVERING	110.9	3.1	104.2	3.0	<0.001*

Note: * significant at 5% level of significance (p<0.05)

The mean systolic blood pressure was comparable between the two groups

FIGURE: MEAN SBP BETWEEN STUDY GROUPS

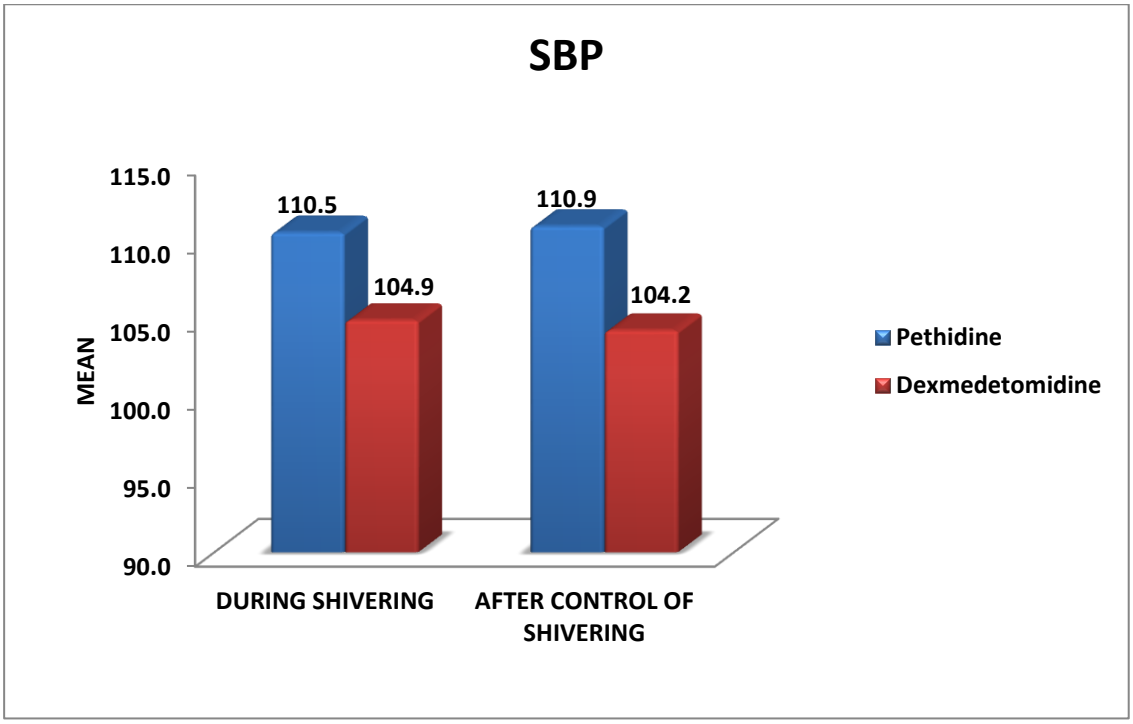


TABLE: MEAN DBP BETWEEN STUDY GROUPS

DBP	Pethidine		Dexmedetomidine		p value
	Mean	SD	Mean	SD	
DURING SHIVERING	70.6	3.2	64.7	3.2	<0.001*
AFTER CONTROL OF SHIVERING	66.7	2.8	62.7	2.5	<0.001*

Note: * significant at 5% level of significance (p<0.05)

The mean diastolic blood pressure was comparable between the two groups

FIGURE: MEAN DBP BETWEEN STUDY GROUPS

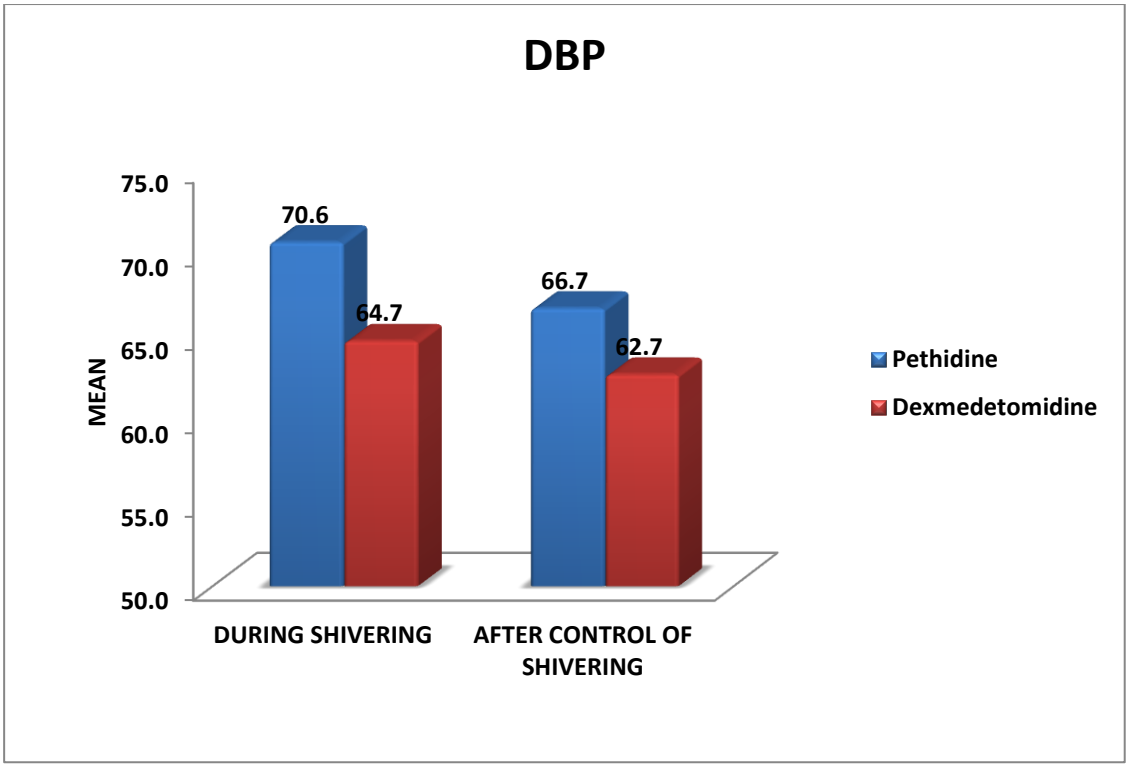


TABLE: POST DRUG COMPLICATIONS BETWEEN STUDY GROUPS

POST DRUG COMPLICATIONS	Pethidine		Dexmedetomidine		p value
	N	%	N	%	
RECURRENCE	6	15	1	2.5	0.048*
NAUSEA	5	12.5	0	0	0.021*
VOMITING	0	0	0	0	-

Note: * significant at 5% level of significance ($p<0.05$)

The incidence of recurrence of shivering and nausea with Pethidine in our study was 15% and 12.5% respectively and was seen Pethidine group.

FIGURE: POST DRUG COMPLICATIONS BETWEEN STUDY GROUPS

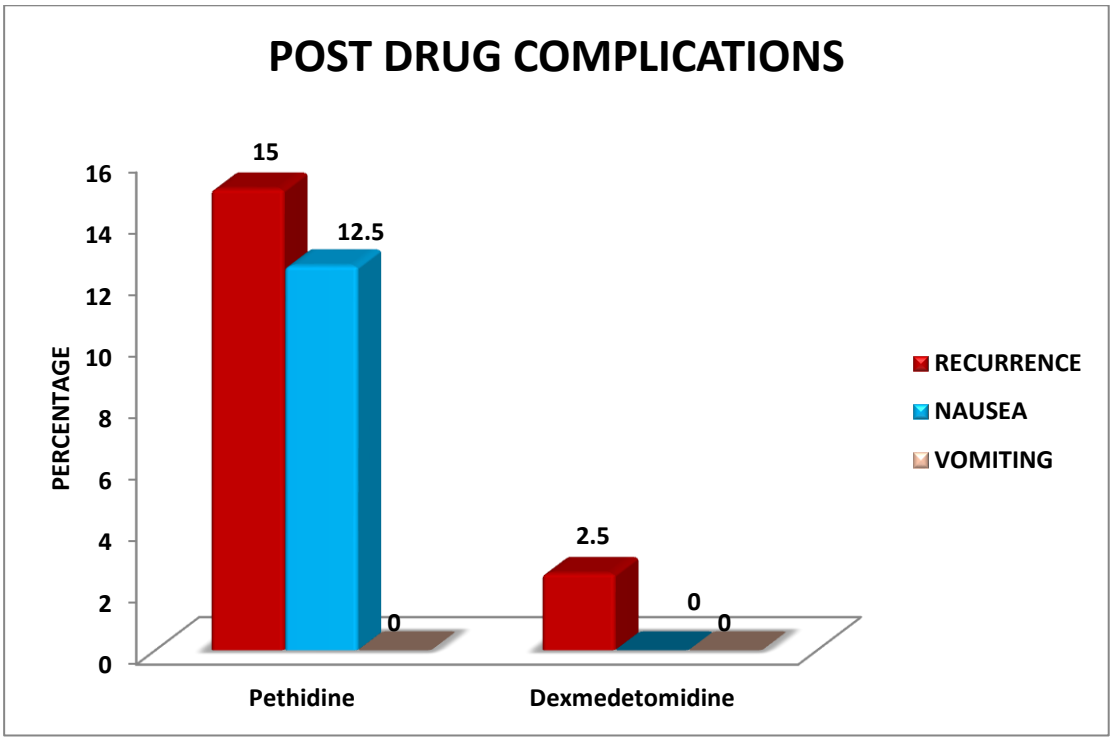


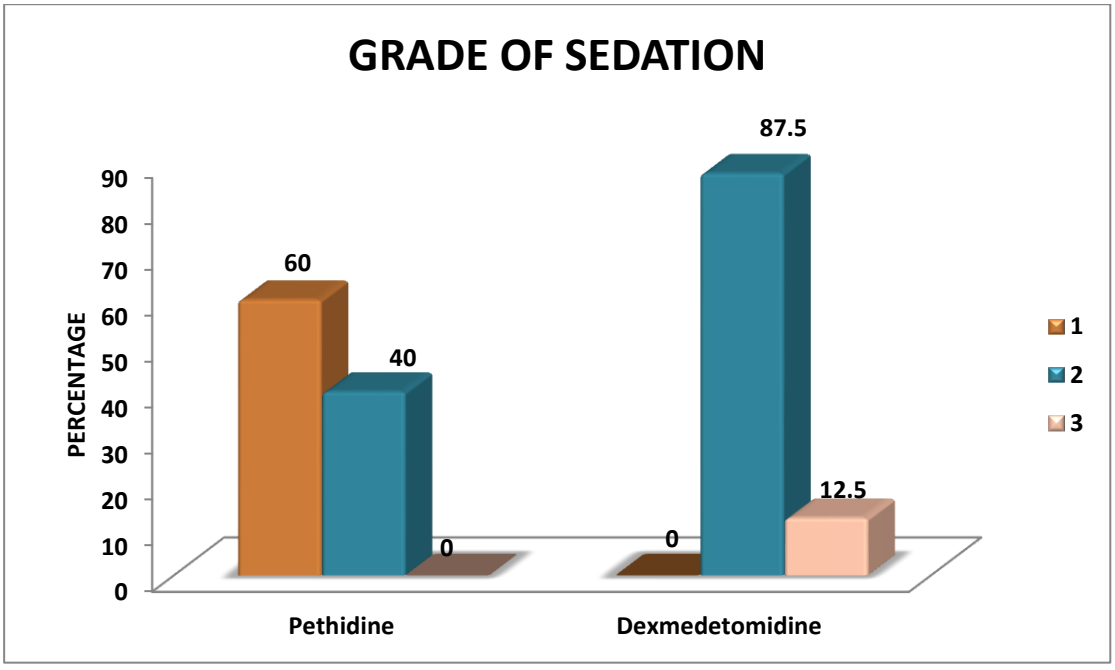
TABLE: GRADE OF SEDATION BETWEEN STUDY GROUPS

GRADE OF SEDATION	Pethidine		Dexmedetomidine		p value
	N	%	N	%	
1	24	60	0	0	<0.001*
2	16	40	35	87.5	
3	0	0	5	12.5	
Total	40	100	40	100	

Note: * significant at 5% level of significance (p<0.05)

The grades of sedation is statistically significant between two groups (P value : <0.001)

FIGURE: GRADE OF SEDATION BETWEEN STUDY GROUPS



Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square (χ^2)/ Freeman-Halton Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. The t test (also called Student's T Test) compares two averages (means) and tells you if they are different from each other. The t test also tells you how significant the differences are. If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analysed using SPSS software v.23.0. and Microsoft office.

DISCUSSION

Spinal anaesthesia is a safe and popular anaesthesia technique used world over for various surgeries. Spinal anaesthesia is a type of central neuraxial blockade, the other commonly used technique being Epidural anaesthesia. The incidence of shivering in patients receiving regional anaesthesia is 19%-33%.**(C K Koay, W Y Chan and M K Chin 1991)(D.J. Buggy and A.W.A. Crossley;2000)** [1,2] The physiologic role of shivering is to provide heat, but its occurrence in relation to anaesthesia is inconsistent and incompletely understood. The probable mechanism under regional anaesthesia could either be a result of decrease in core body temperature, misinformation from receptors or impairment of the physiologic set points **(D.J. Buggy and A.W.A. Crossley;2000)**.[2]

Variety of factors contributes to decrease the core body temperature in patients receiving spinal anaesthesia. These include sympathetic block causing peripheral vasodilation, increased cutaneous blood flow resulting in increased heat loss through skin, cold operating room, rapid i.v infusion of cold i.v fluids, direct effect of cold anaesthetic solution upon the thermo sensitive structures of the spinal cord. **(D.J. Buggy and A.W.A. Crossley;2000) (Jan De Witte, Daniel I.Sessler;2002)** [2,10]

It is difficult to find an appropriate explanation for the effectiveness of pethidine in treating postoperative shivering. It has been reported as effective in treating shaking chills associated with amphotericin B, and granulocyte and platelet infusions. It has also been shown to control shivering in patients undergoing Caesarean section under extradural anaesthesia, by either i.v. or extradural routes . After general anaesthesia, Claybon and Hirch reported that, after general anaesthesia, pethidine 25 mg arrested shivering within 5 min in 73 % of patients. Later, it was

shown to be superior to both morphine and fentanyl in this respect. A more recent study shows that 11 of 14 patients stopped shivering within 5 min after pethidine 25 mg i.v., and that pethidine was effective in reducing the increased metabolic demand of shivering. Our results agree with these studies, in demonstrating the effectiveness of pethidine and suggest that pethidine may be marginally superior to doxapram in this respect. (**P. SINGH, V. DIMITRIOU, R. P. MAHAJAN AND A. W. A. CROSSLEY;1993**) [21]

Dexmedetomidine reduces the vasoconstriction threshold and the shivering threshold and is associated with a lower incidence of shivering **(GERTLE R, BROWN C, MITCHELL D ET AL;2001**) [38] .Alpha‑2 adrenergic agonists are widely used nowadays in anaesthesia and intensive care settings. Dexmedetomidine is an α2 adrenoceptor agonist, with antihypertensive, sedative, analgesic, and anti‑shivering properties.

Dexmedetomidine comparably reduces the vasoconstriction and shivering thresholds, thus suggesting that it acts on the central thermoregulatory system rather than preventing shivering peripherally. **(Talke P, Tayefeh F, Sessler DI;1997)**[59] It has been successfully used as an adjunct to local anaesthetics in spinal anaesthesia and peripheral nerve blockade, for the sedation of mechanically ventilated patients in the Intensive Care Unit, as well as supplementation of post‑operative analgesia. **(Kamibayashi T, Maze M. 2000)** [83] The role of dexmedetomidine in the treatment of shivering has been evaluated in a few studies**. (Derbent A, et al ;2013)** [84] It may be a good choice because of its dual effects related 'anti‑shivering' and sedation.

The demographic parameters between the two groups were comparable, with respect to age, sex height and weight. In our study we recorded temperature using mercury thermometer placed in the vicinity of the Axillary artery. This was as per deductions by **(Daniel I. Sessler;2008)**[5] in his study wherein he concluded that axillary temperatures were fairly good indicator of core body temperature when the thermometer was placed in the vicinity of the Axillary artery, and the patients did not have extremes of thermal perturbations. Following spinal anaesthesia the mean temperature at which shivering occurred in patients in our study was 36.4^{o}C±0.5 for group Dexmedetomidine and 36.4^{o}C±0.4 for group Pethidine. This result was in accordance to study by Aditi Dhimar and associates **(Aditi A. Dhimar, Mamta G. Patel, V.N.Swadia;2008)** [8]

In our study shivering was controlled in 413±16.8 seconds after drug administration in patients in the Pethidine group while it was 205.3±18.1 seconds with patients in Dexmedetomidine group. The results between the two groups were statistically significant with P value (0.00) This result was likely with the study by **Aditi Dhimar and associates** for control intra-operative and post-operative shivering ,complete disappearance of shivering occurred in 5 minutes in Tramadol group when compared with Pethidine group where it took 20 mins which was comparable with our study. In a study **Blaine Easley R, Brady KM, Tobias JD** [12] ,all children had a cessation of shivering behaviour within 5 min following the completion of Dexmedetomidine administration. The onset of effect was 3.5 +/- 0.9 min, which was comparable with our study. In a study by **Geeta Mittal, Kanchan Gupta1, Sunil Katyal, Sandeep Kaushal** [13], control of shivering was 2.52±0.44 in Dexmedetomidine group and 5.92±0.81 in tramadol group which was comparable with our group.

The incidence of nausea and vomiting with Dexmedetomidine in our study was 0%. The results correspond with that of other studies by **Sukhminder Jit Singh Bajwa et al** [85]

In our study the recurrence rate of shivering was 15% seen in Pethidine when compared with 2.5% seen in Dexmedetomidine group which is comparable with **Aditi A. Dhimar** *et al*. [8] reported similar more recurrence rate with Pethidine as in our study (50%) but the dose used in their study was 1 mcg/kg.

SUMMARY

This study was conducted at Shri. B. M. Patil medical college and hospital, Vijayapur between December 2016 to August 2018. This study was designed for the comparison of Pethidine and Dexmedetomidine for the control of intraoperative shivering under spinal anaesthesia. The study was conducted in 80 ASA grade I and II patients of either gender, aged between 20 and 60 years, scheduled for various spinal anaesthesia. The patients were randomised in two groups of 40 patients in each group.

GROUP P – Pethidine 0.5 mg/kg as slow intravenous bolus over 5 minutes.

GROUP D – Dexmedetomidine 0.5mcg/kg as slow intravenous bolus over 10 minutes.

The results were analysed statistically and are represented as follows.

- Dexmedetomidine and Pethidine are effective in treating patients with post-spinal anaesthesia shivering.
- Time taken for control of shivering was shorter with Dexmedetomidine (205.3 $\pm$ 18.1sec) as compared to Pethidine (413 $\pm$ 16.8 sec) with 95% C.I
- Dexmedetomidine causes lesser side effects as compared to Pethidine
- Arousable sedation caused by Dexmedetomidine provides additional comfort to the patients.

CONCLUSION

- Both Dexmedetomidine (0.5mcg/kg) and Pethidine (0.5mg/kg) are effective in treating patients with post spinal anaesthesia shivering but time taken for control of shivering was shorter with Dexmedetomidine as compared to Pethidine.

- Dexmedetomidine causes lesser side effects as compared to Pethidine, arousable sedation caused by Dexmedetomidine provides additional comfort to the patient.

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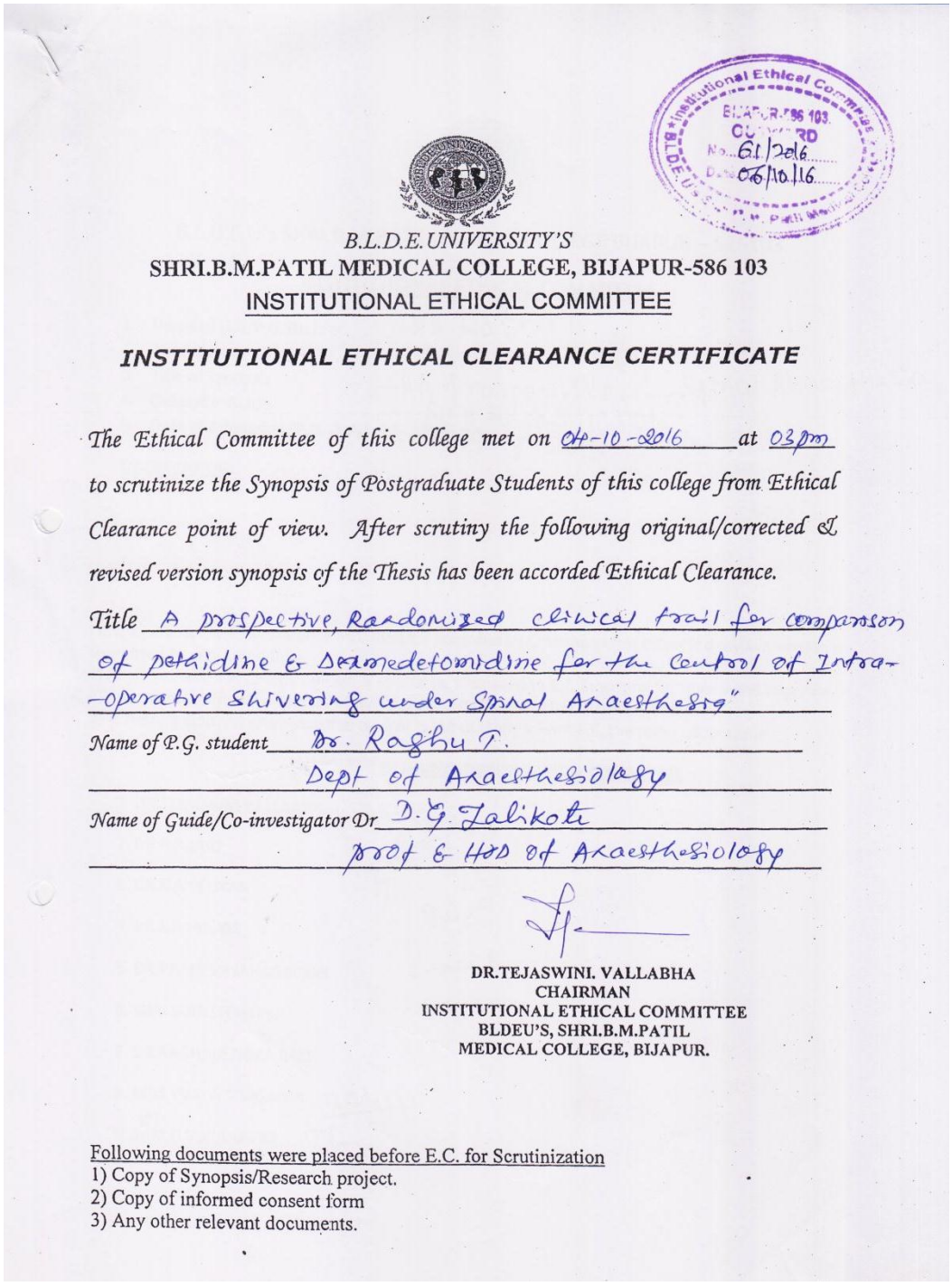
ANNEXURES

ETHICAL CLEARANCE CERTIFICATE



B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 04-10-2016 at 03pm to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title "A prospective, Randomized clinical trail for comparison of pethidine & Dexmedetomidine for the control of Intra-operative shivering under Spinal Anaesthesia"

Name of P.G. student Dr. Raghu T.
Dept of Anaesthesiology

Name of Guide/Co-investigator Dr D.G. Talikoti
Prof & HOD of Anaesthesiology

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

SAMPLE INFORMED CONSENT FORM

INVESTIGATIONS / INTERVENTIONS:

Investigations or interventions required in this study were routine standardized procedures. There were no animal experiments involved in this study.

B.L.D.E.(DEEMED TO BE UNIVERSITY) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR – 586103, KARNATAKA

TITLE OF THE PROJECT	**:**	"A PROSPECTIVE, RANDOMIZED CLINICAL TRIAL FOR COMPARISON OF PETHIDINE AND DEXMEDETOMIDINE FOR THE CONTROL OF INTRAOPERATIVE SHIVERING UNDER SPINAL ANAESTHESIA"
PRINCIPAL INVESTIGATOR	**:**	Dr. RAGHU T Department of Anaesthesiology Email: raghut999@gmail.com
PG GUIDE	**:**	Dr. D. G. TALIKOTI Professor & HOD Dept. of Anaesthesiology B.L.D.E. (DEEMED TO BE University) Shri. B. M. Patil, Medical College Hospital & Research Centre, Vijayapur-586103

PURPOSE OF RESEARCH:

I have been informed that this study is: "A Prospective, Randomized clinical Trial for Comparison of Pethidine and Dexmedetomidine for the control of Intraoperative Shivering under Spinal Anaesthesia"

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I understand that I will be participating in the study**:** "A PROSPECTIVE, RANDOMIZED CLINICAL TRIAL FOR COMPARISON OF PETHIDINE AND DEXMEDETOMIDINE FOR THE CONTROL OF INTRAOPERATIVE SHIVERING UNDER SPINAL ANAESTHESIA"

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience some pain while intubating and I understand that necessary measures will be taken to reduce these complications as and when they arise.

BENEFITS:

I understand that my wards participation in this study will help in: "Knowing the better drug for control of shivering under spinal anaesthesia"

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. If the data are used for publication in the medical literature

or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. Raghu T is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form will be given to me for keep for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. Raghu T will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly due to my participation in this study, such injury will be reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date: Dr. Raghu T

(Investigator)

Patient's signature Witness signature

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr. Raghu T** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

PROFORMA

PATIENT DETAIL: DATE:

I. Name: Age/ Sex: I.P No:

Ward: Group allotted by randomization: Group P / Group D

II. 1. Type of the surgery: Duration of surgery (min):

2. Indication:

III. Significant History:

IV. General Physical Examination:

Pallor Icterus Cyanosis Clubbing Koilonychia

LymphadenopathyOedema

V. Vital Parameters

Pulse Blood Pressure Respiratory Rate Temperature

VI. Systemic Examination

1. CVS 2.RS 3. CNS

VII. Airway Assessment: MP Grade:

Investigations :

- Hb% :
- Total Leucocyte count :
- Differential count :
  - Neutrophils :
  - Lymphocytes :
  - Basophils :
  - Eosinophils :
  - Monocytes :

- Platelet count :
- Bleeding time/ Clotting time :
- Random Blood sugar :
- Urine routine:
- ECG :
- Chest X ray:
- Blood Urea:
- Serum Creatinine:
- Any other :
- ASA Grade :
- Grade of shivering:
- Time from drug administration to control of shivering(min):
- Time from drug administration to disappearance of shivering(min):
- Post drug nausea:
- Post drug vomiting:
- Grade of sedation:
- Recurrence of shivering:
- Drug label:

TIME (MIN)	0	1	2	3	4	5	10	20	30
HEART RATE(B.P.M)									
B.P(mmHg)									
Spo2									

KEY TO MASTER CHART

SI – Serial number

P – Pethidine

D – Dexmedetomidine

A – Age

S – Sex

W – Weight

ASA – American Society of Anaesthesiologist grade

Tp – Temperature preoperatively

D – Duration which shivering first noticed

G – Grade of shivering

Ts – Temperature during shivering

Hr-s – Heart rate during shivering

B-s – B.P during shivering

Sp-s – Spo2 during shivering

Ct – Time required to control shivering post study drug administration

Hr-c – Heart rate following shivering control

Bp-c – B.P following control of shivering

Sp-c – Spo2 following shivering control

N/V – Nausea/Vomiting

R – Recurrence

GOS – Grades of sedation

Dis – Complete disappearance of shivering