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Comparative study between butorphanol and clonidine in intraoperative shivering during subarachnoid block

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Abstract
Shivering presents as a common perioperative problem causing hypertension, tachycardia and increased metabolic demands. It also interferes with intra-operative monitoring of electrocardiogram, BP, and oxygen saturation. Various risk factors associated with shivering include type and duration of anesthesia, level of sensory blockade, age, temperature of the operating room, and infusion fluids. Hence the present study was planned for clinical outcomes of the patients of intraoperative shivering under spinal anesthesia by comparative administration of Butorphanol and Clonidine.
The present study was conducted in Department of Anesthesia, Government Medical College, Bettiah, Bihar, India. The 40 cases underwent the surgeries of lower limb fractures, infra-umblical and urological surgeries. The cases were divided in two study groups. In Group I cases intraoperatively shivering was treated with intravenous Butorphanol 0.015mg/ kg. In Group II cases intraoperatively shivering was treated with intravenous Clonidine 0.5 mg /Kg. The efficacy and response rate of the study drugs were evaluated and recorded. Side effects like, nausea, vomiting, hypotension, sedation were recorded.
The data generated from the present study concludes that complete control of post-operative shivering with less or no severe side effects was achieved with Butorphanol in comparisons to clonidine. Butorphanol was found to be safe and effective in prevention and treatment of post-operative shivering with no hemodynamic, cardio respiratory side effect in comparison to Clonidine.

Keywords: butorphanol, clonidine, spinal anaesthesia, shivering, etc

Introduction
Spinal anaesthesia also called subarachnoid block and intrathecal block [1], is a form of neuraxial regional anaesthesia involving the injection of a local anaesthetic or opioid into the subarachnoid space, generally through a fine needle, usually 9 cm (3.5 in) long. It is a safe and effective form of anesthesia which can be used as an alternative to general anesthesia commonly in surgeries involving the lower extremities and surgeries below the umbilicus. The local anesthetic or opioid injected into the cerebrospinal fluid provides anesthesia, analgesia, and motor and sensory blockade. The tip of the spinal needle has a point or small bevel. Recently, pencil point needles have been made available (Whitacre, Sprotte, Gertie Marx and others) [2].
Spinal anaesthesia is a commonly used technique, either on its own or in combination with sedation or general anaesthesia. It is most commonly used for surgeries below the umbilicus, however recently its uses have extended to some surgeries above the umbilicus as well as for postoperative analgesia.
Spinal anaesthesia is the technique of choice for Caesarean section as it avoids a general anaesthetic and the risk of failed intubation (which is probably a lot lower than the widely quoted 1 in 250 in pregnant women [3]. The post-operative analgesia from intrathecal opioids in addition to non-steroidal anti-inflammatory drugs is also good. Spinal anesthesia is a favorable alternative, when the surgical site is amenable to spinal blockade, for patients with severe respiratory disease such as COPD as it avoids potential respiratory consequences of intubation and ventilation. It may also be useful, when the surgical site is amenable to spinal blockade, in patients where anatomical abnormalities may make tracheal intubation very difficult. In pediatric patients, spinal anesthesia is particularly useful in children with difficult airways and those who have are poor candidates for endotracheal anesthesia such as increased respiratory risks or presence of full stomach [4]. This can also be used to effectively treat and prevent pain following surgery, particularly thoracic, abdominal pelvic, and lower extremity orthopedic procedures [5].
Complications of spinal anesthesia can result from the physiologic effects on the nervous system and can also be related to placement technique. Most of the common side effects are minor and are self-resolving or easily treatable while major complications can result in more serious and permanent neurological damage and rarely death. These symptoms can occur immediately after administration of the anesthetic or arise up to 48 hours after surgery.
Regardless of the anaesthetic agent (drug) used, the desired effect is to block the transmission of afferent nerve signals from peripheral nociceptors. Sensory signals from the site are blocked, thereby eliminating pain. The degree of neuronal blockade depends on the amount and concentration of local anaesthetic used and the properties of the axon. Thin unmyelinated C-fibres associated with pain are blocked first, while thick, heavily myelinated A-alpha motor neurons are blocked moderately. Heavily myelinated, small preganglionic sympathetic fibers are blocked last. The desired result is total numbness of the area. A pressure sensation is permissible and often occurs due to incomplete blockade of the thicker A-beta mechanoreceptors. This allows surgical procedures to be performed with no painful

sensation to the person undergoing the procedure.

Some sedation is sometimes provided to help the patient relax and pass the time during the procedure, but with a successful spinal anaesthetic the surgery can be performed with the patient wide awake.

In spinal anesthesia, the needle is placed past the dura mater in subarachnoid space and between lumbar vertebrae. In order to reach this space, the needle must pierce through several layers of tissue and ligaments which include the supraspinous ligament, interspinous ligament, and ligamentum flavum. Because the spinal cord (conus medullaris) is typically at the L1 or L2 level of the spine, the needle should be inserted below this between L3 and L4 space or L4 and L5 space in order to avoid injury to the spinal cord.

Patient positioning is essential to the success of the procedure and can affect how the anesthetic spreads following administration. There are 3 different positions which are used: sitting, lateral decubitus, and prone. The sitting and lateral decubitus positions are the most common.

Sitting- The patient sits upright at the edge of the exam table with their back facing the provider and their legs hanging off the end of the table and feet resting on a stool. Patients should roll their shoulders and upper back forward. Lateral decubitus- In this position, the patient lays on their side with their back at the edge of the bed and facing the provider. The patient should curl their shoulder and legs and arch out their lower back. Prone- The patient is positioned face down and their back facing upwards in a jack knife position.

Spinal anaesthetics are typically limited to procedures involving most structures below the upper abdomen. To administer a spinal anaesthetic to higher levels may affect the ability to breathe by paralysing the intercostal respiratory muscles, or even the diaphragm in extreme cases (called a "high spinal", or a "total spinal", with which consciousness is lost), as well as the body's ability to control the heart rate via the cardiac accelerator fibres. Also, injection of spinal anaesthesia higher than the level of L1 can cause damage to the spinal cord, and is therefore usually not done.

Shivering (also called shuddering) is a bodily function in response to cold in humans and other warm-blooded animals. When the core body temperature drops, the shivering reflex is triggered to maintain homeostasis. Skeletal muscles begin to shake in small movements, creating warmth by expending energy. Shivering can also be a response to a fever, as a person may feel cold. During fever the hypothalamic set point for temperature is raised. The increased set point causes the body temperature to rise (pyrexia), but also makes the patient feel cold until the new set point is reached. Severe chills with violent shivering are called rigors. Rigors occur because the patient's body is shivering in a physiological attempt to increase body temperature to the new set point.

Located in the posterior hypothalamus near the wall of the third ventricle is an area called the primary motor center for shivering. This area is normally inhibited by signals from the heat center in the anterior hypothalamic-preoptic area but is excited by cold signals from the skin and spinal cord. Therefore, this center becomes activated when the body temperature falls even a fraction of a degree below a critical temperature level [6].

Increased muscular activity results in the generation of heat as a byproduct. Most often, when the purpose of the muscle activity is to produce motion, the heat is wasted energy. In shivering, the heat is the main intended product and is utilized for warmth.

Newborn babies, infants, and young children experience a greater (net) heat loss than adults because they cannot shiver to maintain body heat [citation needed]. They rely on non-shivering thermogenesis. Children have an increased amount of brown adipose tissue (increased vascular supply, and high mitochondrial density), and, when cold-stressed, will have greater oxygen consumption and will release norepinephrine. Norepinephrine will react with lipases in brown fat to break down fat into triglycerides. Triglycerides are then metabolized to glycerol and non-esterified fatty acids. These are then further degraded in the needed heat-generating process to form CO2 and water. Chemically, in mitochondria the proton gradient producing the proton electromotive force that is ordinarily used to synthesize ATP is instead bypassed to produce heat directly [7].

Shivering, a common post-anaesthesia occurrence is defined as an involuntary, repetitive activity of skeletal muscles. The incidence of shivering has been found to be quite high, approximately 40-50% in different studies [8]. It can double or even triple oxygen consumption and carbon dioxide production [9]. Shivering also increases intraocular and intracranial pressure, and may contribute to increased wound pain, delayed wound healing, and delayed discharge from post-anaesthetic care [10, 11]. Apart from being an uncomfortable experience, its deleterious effects deserve primary prevention and rapid control on occurrence.

Shivering is a physiological response to core hypothermia in an attempt to raise the metabolic heat production. The main causes of intra/post-operative shivering are temperature loss, increased sympathetic tone, pain, and systemic release of pyrogens. Spinal anaesthesia significantly impairs the thermoregulation system by inhibiting tonic vasoconstriction, which plays a significant role in temperature regulation. It also causes a redistribution of core heat from the trunk (below the block level) to the peripheral tissues. These factors predispose patients to hypothermia and shivering [12].

The treatment of shivering includes both pharmacological and non-pharmacological methods. The non-pharmacological management is by external heating like the use of forced air warming, warming blankets, warmed fluids etc., According to the results of a meta-analysis, the most frequently reported pharmacological interventions include clonidine, pethidine, tramadol, nefopam and ketamine [13]. Unfortunately, no gold standard treatment is known for shivering as the administration of all the available drugs is associated with various adverse effects.

The most common indication for butorphanol is management of migraine using the intranasal spray formulation. It may also be used parenterally for management of moderate-to-severe pain, as a supplement for balanced general anesthesia, and management of pain during labor. Butorphanol is also quite effective at reducing post-operative shivering (owing to its Kappa agonist activity).

Clonidine is used to treat high blood pressure, attention deficit hyperactivity disorder (ADHD), drug withdrawal (alcohol, opioids, or smoking), menopausal flushing, diarrhea, and certain pain conditions. Clonidine may be effective for lowering blood pressure in people with resistant hypertension. Clonidine works by slowing the

pulse rate and exert a reduction of serum concentrations of renin, aldosterone and catecholamines.

Shivering presents as a common perioperative problem causing hypertension, tachycardia and increased metabolic demands. It also interferes with intra-operative monitoring of electrocardiogram, BP, and oxygen saturation. Various risk factors associated with shivering include type and duration of anesthesia, level of sensory blockade, age, temperature of the operating room, and infusion fluids. Hence the present study was planned for clinical outcomes of the patients of intraoperative shivering under spinal anesthesia by comparative administration of Butorphanol and Clonidine.

Methodology

The present study was conducted in Department of Anesthesia, Government Medical College, Bettiah, Bihar, India. The 40 cases underwent the surgeries of lower limb fractures, infra-umblical and urological surgeries. The cases were divided in two study groups. In Group I cases intraoperative shivering was treated with intravenous Butorphanol 0.015mg/ kg. In Group II cases intraoperative shivering was treated with intravenous Clonidine 0.5 mg /Kg. The efficacy and response rate of the study drugs were evaluated and recorded. Side effects like, nausea, vomiting, hypotension, sedation were recorded.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Upon arrival in the operation theatre, an 18G venous cannula was inserted and preloading done with Ringer′s Lactate solution 10 ml/kg before giving spinal anaesthesia and maintained at 6 ml/kg/h after spinal anaesthesia. Before starting the procedure, standard monitors were attached and all the baseline parameters such as heart rate (HR), non-invasive blood pressure (NIBP), oxygen saturation (SPO 2), electrocardiography (ECG), and body temperature (axillary) were recorded. Subarachnoid anaesthesia was administered with 0.5% heavy bupivacaine (15 mg) at L 3-4 or L 4-5 interspace using 26G Quincke′s spinal needle under aseptic conditions. All operation theatres were maintained at an ambient temperature of around 24°C-25°C. Supplemental oxygen was administered to all the patients at the rate of 5 l/min with face mask and patients were covered with drapes but not actively warmed. IV fluids and anaesthetics were administered at room temperature. Vital parameters such as HR, NIBP, and SPO 2 were recorded at intervals of every 5 min for first 30 min and every 15 min for the rest of the observation period. Continuous ECG monitoring was done.

Results & Discussion

Intra and post-operative shivering is a distressing experience for the patient. The exact mechanism of shivering during spinal anaesthesia has not been fully recognized. The possible mechanisms include impairment of central thermoregulation, internal redistribution of body heat, and heat loss to the environment. Potential risk factors for hypothermia in spinal anaesthesia include ageing, level of sensory block, temperature of the operation theatre and IV solutions.

In this study, all operation theatres (OTs) maintained an ambient temperature of 23-25°C, and all fluids and drugs were at room temperature during the surgery. Demographic factors such as age, gender, duration of anaesthesia and surgery have also been matched to reduce any confounding bias.

The neurotransmitter pathways involved in shivering are multiple and involve opioids, α2 adrenergic, serotenergic, and anticholinergic receptors. Hence, drugs acting on these systems which include opioids (pethidine, nalbuphine, or tramadol), ketanserin, propofol, doxapram, clonidine, ketamine and nefopam are utilized in the treatment of shivering. However, adverse effects such as hypotension, hypertension, sedation, respiratory depression, nausea and vomiting limit their use. Hence, the hunt for an ideal anti-shivering agent is continuing.

Anaesthesia carries two dreaded side effects, one is hypotension and another is shivering. Ironically every anaesthesiologist and allied persons are well prepared to deal with the hypotension and every pre and Para operative arrangement and precautions are taken to counter it because it may become life threatening, whereas shivering is least taken care off unless it appears, though it happens in 40-70% of cases, and is very agonizing to the patient. Various pharmaceutical agents are being used to treat it though the most effective with least ADR's is not yet determined.

Table 1: Basic Characteristics

Groups	**Group I**	**Group II**
Administration of	**Butorphanol 0.015mg/ kg**	**Clonidine 0.5 mg /Kg**
No. of Cases	20	20
Age (years)	23 – 48	27 – 45
Sex		
Male	11	15
Female	9	5
BMI (Kg/m2)	20.3 – 23.7	21.4 – 23.8
Physical status		
ASA I	14	15
ASA II	6	5
Duration of Surgery, (mins)	61 - 104	69 – 114
Baseline axillary temperature ° C	35.4 – 37.3	36.1 – 37.2
Shivering grade		
Grade III	11	10
Grade IV	9	10

Table 2: Anti-shivering effects

Groups	**Group I**	**Group II**
Administration of	**Butorphanol 0.015mg/ kg**	**Clonidine 0.5 mg /Kg**
No. of Cases	20	20
Mean time for onset of shivering (minutes)	11 – 15	10 – 15
Time for control of shivering (seconds)	42 – 116	264 – 384
Control of Shivering (cases)		
Complete	16	11
Incomplete	2	7
Failure	2	2
Recurrence rate (cases)	2	9
Sedation		
Present	8	9
Absent	12	11

Table 3: Side Effects

Groups	Group I	Group II
Administration of	**Butorphanol 0.015mg/ kg**	**Clonidine 0.5 mg /Kg**
No. of Cases	20	20
Itching	0	0
Nausea/Vomiting	1	2
Respiratory depression	0	0
Hypotension	0	4
Bradycardia	0	4

Various studies have established the role of clonidine as an antishivering agent. During some of the related studies, sedative effects of clonidine were noticed when a dose of 3 μg/kg was used [14, 15]. However, some studies revealed that even a lower dose of clonidine was effective in the reduction of shivering [16].

Clonidine was found to be inferior to tramadol and butorphanol in the control of shivering with a higher rate of recurrence. A higher fall in systolic and diastolic BP and an increase in heart rate was found in the clonidine group after treatment of shivering than in other two groups [17].

Shukla *et al*. compared the effects of clonidine and tramadol in shivering control and found that shivering got controlled earlier with clonidine than tramadol. Two patients of clonidine group and one patient in tramadol group developed bradycardia. Three patients in clonidine group developed hypotension [18].

Joshi *et al*. observed that tramadol and butorphanol were similar in their ability to control shivering under spinal anesthesia in contrast to our study where butorphanol was superior to tramadol, which was statistically significant. There was no difference in hemodynamic parameters in all the three groups pre-shivering, intra-shivering, or post-shivering [19].

Butorphanol was quicker than pethidine in abolishing shivering successfully. Relapse is more in pethidine than butorphanol [20].

Conclusion

The data generated from the present study concludes that complete control of post-operative shivering with less or no severe side effects was achieved with Butorphanol in comparisons to clonidine. Butorphanol was found to be safe and effective in prevention and treatment of post-operative shivering with no hemodynamic, cardio respiratory side effect in comparison to Clonidine.

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