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Comparative assessment of control of intraoperative shivering by administration of butorphanol and clonidine under spinal anesthesia

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Abstract
Shivering presents as a common perioperative problem causing increased metabolic demands, tachycardia and hypertension. It also interferes with routine monitoring like ECG, blood pressure and pulse oximerty. Shivering is seen approximately 40-60% after volatile anesthetics. It has also been observed that around 30% of patients under epidural anaesthesia develop shivering. Intra and post-operative shivering is distressing and unpleasant experience for the patient. The exact mechanism of shivering during spinal anaesthesia is not very clear. The possible reasons could be internal redistribution of heat from core to periphery, impaired central thermoregulatory mechanisms, peripheral vasodilatation and heat loss to the environment. Hence based on above findings the present study was planned for Comparative Assessment of Control of Intraoperative Shivering by Administration of Butorphanol and Clonidine under Spinal Anesthesia.

The present study was planned in Department of Anaesthesia, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar. In the present study 30 cases of the patients undergoing the surgeries of lower limb fractures, infra-umblical and urological surgeries under spinal anesthesia were enrolled. The 15 cases in Group B received an iv bolus of 1 mg (1 mL) Butorphanol. The 15 cases in Group C received an iv bolus of 150 µg (1 mL) clonidine. Further interventions and monitoring were done by an investigator blinded to the group allocation.

The data generated from the present study concludes that Control of shivering is faster and better with Butorphanol than Clonidine. The incidence of recurrence is significantly less with Butorphanol than Clonidine. The incidence of hemodynamic variations (bradycardia / hypotension) is significantly higher with Clonidine as compared to Butorphanol.

Keywords: intraoperative shivering, butorphanol, clonidine under spinal anesthesia, etc

Introduction

Spinal anaesthesia also called spinal block, 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 performed by anesthesiologists 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].

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.

Subarachnoid (spinal) block is a safe and effective alternative to general anesthesia when the surgical site is located on the lower extremities, perineum (eg, surgery on the genitalia or anus), or lower body wall (eg, inguinal herniorrhaphy). Because of the technical challenges of readily identifying the epidural space and the toxicity associated with the large doses of local anesthetics needed for epidural anesthesia, spinal anesthesia was the dominant form of neuraxial anesthesia well into the 20th century [1].

Subarachnoid block can be used as the sole source of anesthesia. Alternatively, spinal and epidural anesthesia can be used jointly, taking advantage of the qualities of both techniques: the rapid, dense sensorimotor blockade of a spinal anesthetic and the opportunity to redose the patient with an epidural catheter anesthetic [2].

Spinal anesthesia produces intense sensory and motor

blockade as well as sympathetic blockade. As opposed to epidural anesthesia, in which medications are instilled outside the dura mater, the goal of spinal anesthesia is to instill the desired medications into the cerebrospinal fluid (CSF). The sensorimotor block produced requires smaller doses of local anesthetics (hence, local anesthetic toxicity is rarely a concern) and is often more dense in character.

Although the focus of this topic is subarachnoid block, comparison with epidural anesthesia may be informative. For instance, brief periods (less than 24 hours) of postoperative analgesia can be facilitated by adding an opioid to the local anesthetic injected into the cerebrospinal fluid. Prolonged postoperative analgesia is best ensured by insertion of an epidural catheter, using an opioid and local anesthetic combination infused continuously over the first few postoperative days. See the table below for a comparison of subarachnoid and epidural anesthesia.

Spinal anesthesia is a safe and effective alternative to general anesthesia when the surgical site is located on the lower extremities, perineum (eg, surgery on the genitalia or anus), or lower body wall (eg, inguinal herniorrhaphy). Cesarean deliveries are routinely performed under spinal anesthesia, as are total hip arthroplasty and total knee arthroplasty [3, 4].

Advantages include avoidance of general anesthesia and the airway management concerns that accompany general anesthesia. However, that is not to suggest that spinal anesthesia is always the best course in a patient likely to have difficulties with endotracheal intubation. All patients with difficult airways, no matter what anesthetic plan is chosen, should have a well thoughtout plan for airway management, should it be needed.

Additional benefits may include reducing the metabolic stress response to surgery, reduction in blood loss, decrease in the incidence of venous thromboembolism, reduction in pulmonary compromise (particularly in patients with advanced pulmonary disease), and the ability to monitor the patient's mental status.

Strong contraindications include patient refusal, lack of patient cooperation, difficulties with positioning, and increased intracranial pressure. Other contraindications include situations that require some risk-benefit analysis include hypovolemia, coagulation disturbances, stenotic valvular disease, bacteremia, and infection at the site of needle insertion.

Spinal anesthesia has also been noted to result in symptomatic deterioration in patients with multiple sclerosis [5]. Patients with chronic low back pain may decline spinal anesthesia out of concerns for increased low back pain. Performing spinal anesthesia in patients with degenerative lumbar spine disease or a prior history of lumbar surgery may prove technically difficult, but these are not necessarily contraindications.

Allergy to local anesthetics may also be a contraindication, but true allergies are usually found with ester-based local anesthetics (eg, tetracaine), not the amide-based local anesthetics (eg, bupivacaine), so finding a suitable local anesthetic is not challenging [6, 7].

Although one-shot injection techniques are the norm, continuous spinal anesthesia has enjoyed periods of popularity while also being demonized. In the early 1990s, spinal microcatheters (27-G) were introduced but were followed by an increased incidence of postoperative cauda equina syndrome [8]. In cases in which cauda equina syndrome developed postoperatively, microcatheters were used; in response to an unsuitable rise in anesthetized dermatomal levels, unusually large of doses of local anesthetics (usually lidocaine) were administered to effect a sufficient spinal anesthetic.

What may have happened was that insufficient turbulence was created through injection through the microcatheter, the local anesthetic pooled distally in the lumbar intrathecal space (below the natural lumbar lordosis), and with repeated local anesthetic doses, administered in hopes of advancing the dermatomal level of local anesthetic effect, toxic local anesthetic levels were created in the region of the cauda equina.

Continuous spinal techniques may be regaining a slow resurgence in popularity, but patients should be carefully chosen. Instead of microcatheters, larger conventional epidural catheters should be used. Because of the larger rent in the dura, postdual puncture headache is an increased risk; therefore, patients who are less likely to have postdual puncture headache, such as older patients, are better candidates. The wisdom that excessive doses of local anesthetics are best not injected into the intrathecal space has been hard earned [9].

With any sympathectomy, blood pressure is expected to decrease secondary to increased venous capacitance and decreased peripheral vascular resistance. Incidence of hypotension is estimated at 35%. Bradycardia secondary to blockade of sympathetic-mediated cardioaccelerator nerves (T1-T4) may contribute to decreased cardiac output. The incidence is around 13%, and bradycardia is more likely to be found in children or adults with baseline heart rates less than 60 per minute and may be reversed with the anticholinergic medications atropine or glycopyrrolate.

Even in patients with ischemic heart disease, cardiac output appears maintained [10]. It is important but as yet unclear what level of blood pressure is appropriate under subarachnoid block. As this remains unclear, practitioners will invariably choose to support the patient's blood pressure through use of vasopressor medications (the mixed alpha- and beta-agonist ephedrine and/or the alpha-agonist phenylephrine) and intravenous fluids. However, the value of intravenous fluid resuscitation in supporting blood pressure has been in dispute [11]. Perhaps because of the rapid redistribution of crystalloid out of the intravascular space, preloading the patient with these solutions may have minimal benefit for prevention hypotension. Prehydration with colloid solutions may be more effective. In a study of pregnant patients undergoing spinal anesthesia for cesarean section, having patients sit up for 5 minutes before placing them supine reduced requirements for intravenous fluids andephedrineanddecreased nausea, vomiting and dyspnea [12].

Tidal volumes tend to remain unchanged during subarachnoid block, although expiratory reserve is diminished secondary to paralysis of abdominal musculature. The gut is contracted due to unopposed parasympathetic activity. Hyperperistalsis may contribute to nausea and vomiting but, perhaps more commonly, nausea and vomiting are indicators of hypotension. Renal function is preserved.

Although hypotension and bradycardia are most likely to occur soon after performance of the subarachnoid block, the vasodilated state persists throughout the spinal anesthetic. Hence, blood loss secondary to the surgical procedure must

be closely monitored and replaced with a balanced crystalloid or colloid solution or packed red blood cells if the blood loss is severe.

Major complications with subarachnoid block are rare [13]. Should local anesthetic reach the brainstem, the patient may develop dysphonia, dyspnea, progressive upper extremity weakness, experience loss of consciousness and loss of airway protection, and require definitive airway control. Hypotension, bradycardia, and cardiac arrest are also risks. Respiratory arrest may be secondary to hypoperfusion of brainstem respiratory centers. Pupillary dilation in the setting of loss of consciousness suggested the diagnosis of "total spinal."

Once the airway is controlled and the patient mechanically ventilated, attention should be directed towards addressing significant changes in heart rate or blood pressure as described previously. Total spinals tend to be short in duration; not uncommonly, once the surgery is complete the total spinal has resolved, the patient's mentation has returned, and the patient may be extubated.

Concerningly, patients under spinal anesthesia are more sensitive to sedation and are at increased risk of respiratory depression. Caplan *et al* published a review of otherwise healthy patients who experienced cardiorespiratory arrest [14]. Despite being otherwise healthy and having witnessed cardiac arrest, outcomes were devastating. Many died and most of the remainder were discharged to assisted living settings with persistent neurologic complications. This altered sensitivity to sedative medications was later verified [15]. The purported mechanism was loss of peripheral input into the brainstem center responsible for maintaining arousal (the reticular activating system).

Caplan *et al* also identified the difficulty in resuscitating patients under spinal anesthesia. These vasodilated patients do not respond to conventional doses of pressor medications as outlined in traditional Advanced Cardiac Life Support algorithms and are a reflection of basically different mechanisms leading to cardiac arrest in the perioperative environment [16].

Other complications include direct injury to spinal nerves, postdural puncture headache, neuraxial hematoma, meningitis or neuraxial abscess, adhesive arachnoiditis and cauda equina syndrome, and transient neurologic syndrome. Because these patients become vasodilated, they are at risk for hypothermia; active warming measures should be employed on these patients just as they are in patients receiving general anesthesia. The hypothermia is due to vasodilation as well as loss of thermoregulation.

The incidence of postdural puncture headaches after spinal anesthesia is about 1%. Because of the larger needles used for epidural anesthetics, the incidence of postdural puncture headaches (should the dura mater be pierced) is higher with epidural anesthetics. Postdural puncture headaches are associated with leakage of cerebrospinal fluid. They tend to be intense, positional (worse when upright), and often localized to the occipital region and neck. Diplopia (thought secondary to traction on the sixth cranial nerve) and blurred vision may be reported. The frequency is increased in women, younger patients, parturients, and obese patients.

The incidence of postdural puncture headaches with spinal anesthesia has been decreasing recently due to changes in the shape of spinal needles. Previously, the needles were beveled, but now they tend to be shaped like a pencil point. The rent in the dura is associated with less leakage of cerebrospinal fluid.

Before the diagnosis of postdural puncture headache is made, other causes of severe headache (hypertension or other central nervous system maladies) should be considered and pursued if necessary. Treatment of postdural puncture headache consists of hydration, analgesics, and caffeine, given either orally or parentally. If conservative therapy fails, epidural blood patches are indicated and result in improvement in headache in over 90% of patients affected [17].

Much attention has been given to considering whether spinal (or epidural) anesthesia is appropriate in patients receiving anticoagulants. The American Society of Regional Anesthesia has led educational efforts in this regard [18]. Whether regional anesthesia can be safely undertaken while the patient is anticoagulated is a function of the dose of the particular medication and frequency of dosing, whether more than one anticoagulant is being administered concurrently, and the time since the last anticoagulant dose.

The principal sites of effect are the spinal cord and spinal nerve roots. Reabsorption of the injected agents from the cerebrospinal fluid into the systemic circulation limits the duration of effect. Vasocontrictor agents such as epinephrine may delay reabsorption and prolong local anesthetic effect.

Baricity is defined as the ratio of densities of two solutions. In this situation, the density of the local anesthetic solution is compared to the density of cerebrospinal fluid. Solutions that are hyperbaric relative to the density of cerebrospinal fluid tend to sink more than isobaric or hypobaric solutions. The local anesthetic chosen is based on the anticipated duration of surgery. Concerns about lidocaine producing transient neurologic syndrome are discussed in Complications.

Patient characteristics that influence the duration of local anesthetic effect include height, position when injecting, intra-abdominal pressure, anatomic features of the spinal canal, and pregnancy. Lumbosacral cerebrospinal fluid volumes have been noted to vary remarkably (approximately 30-80 mL) and are definitely decreased during pregnancy. Of all these features, cerebrospinal fluid volume is believed to probably be the most important factor in determining the extent of blockade as well as its time to regression.

Opioids are frequently added to local anesthetics. They prolong the duration of anesthesia without remarkably increasing motor blockade or sympathetic blockade and provide postoperative analgesia as well. Major sites of action are the opioid receptors within the second and third laminae of the substantia gelatinosa of the doral horn of the spinal cord.

The hydrophilic opioid morphine has a longer and more diffuse duration of effect (6-24 hours) when compared to the lipophilic opioids fentanyl and sufentanil (about 4 hours or slightly more). Side effects of all opioids include respiratory depression, nausea and vomiting, pruritus, and urinary retention. These side effects may be reversed with opioid agonists or mixed agonist-antagonist, but this may reverse analgesia as well.

A useful landmark is the line from the top of both iliac crests, which coincides with the L3-L4 interspace. Either a midline or paramedian approach can be used.

The patient may be placed in either the lateral decubitus position or sitting up with support from an assistant. Many

favor the sitting position because it facilitates more accurate identification of the spinal anatomy. This position is definitely preferred when only dense blockade of the perineal anatomy is needed. However, an advantage of the decubitus position is the ability to more easily sedate the patient. Occasionally, spinal anesthetics are performed in the prone position. The patient is asked to curl his or her back dorsally, opening up the vertebral interspaces.

The goal is to inject the chosen medication(s) into the cerebrospinal fluid-filled subarachnoid space. To achieve this, the spinal needle will pass through skin, subcutaneous tissue, supraspinous ligament, interspinous ligament, ligamentum flavum, dura mater, and subarachnoid membrane.

Shivering presents as a common perioperative problem causing increased metabolic demands, tachycardia and hypertension. It also interferes with routine monitoring like ECG, blood pressure and pulse oximerty. Shivering is seen approximately 40-60% after volatile anesthetics. It has also been observed that around 30% of patients under epidural anaesthesia develop shivering. Intra and post-operative shivering is distressing and unpleasant experience for the patient. The exact mechanism of shivering during spinal anaesthesia is not very clear. The possible reasons could be internal redistribution of heat from core to periphery, impaired central thermoregulatory mechanisms, peripheral vasodilatation and heat loss to the environment [19]. Hence based on above findings the present study was planned for Comparative Assessment of Control of Intraoperative Shivering by Administration of Butorphanol and Clonidine under Spinal Anesthesia.

Aim & Objective

To control assessment of Assessment of Control of Intraoperative Shivering by Administration of Butorphanol (1 ml) and Clonidine (1 ml) IV in patients undergoing surgery of Spinal Anesthesia.

Methodology

The present study was planned in Department of Anaesthesia, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar. In the present study 30 cases of the patients undergoing the surgeries of lower limb fractures, infra-umblical and urological surgeries under spinal anesthesia were enrolled. The 15 cases in Group B received an IV bolus of 1 mg (1 mL) Butorphanol. The 15 cases in Group C received an IV bolus of 150 µg (1 mL) clonidine. Further interventions and monitoring were done by an investigator blinded to the group allocation.

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.

Results & Discussion

The exact cause of shivering under spinal anaesthesia is not well understood. Spinal anaesthesia prevents peripheral vasoconstriction and increases cutaneous heat loss. The threshold for vasoconstriction and shivering is decreased by 0.6°C above the level of block and this reduction is directly proportional to the number of segments blocked [20, 21]. Spinal anaesthesia causes redistribution of heat from core (below the level of block) To periphery due to spinal induced vasodilatation [22]. All these factors under spinal anaesthesia cause shivering and predispose patients to hypothermia. Other causes of shivering include- pre-existing fever or septicemia, cold temperature of operation theatre, rapid infusion of cold or contaminated IV fluids, drug allergies, blood transfusion reactions, etc.

Unfortunately, shivering presents as a common perioperative problem causing hypertension, tachycardia, and increased metabolic demands. It also interferes with intraoperative monitoring of electrocardiogram, blood pressure, and pulse oxygen saturation [23]. Various risk factors associated with shivering include type and duration of anesthesia, level of sensory blockade, age, and temperature of the operating room and infusion fluids [24]. Postoperative shivering occurred in 5%–65% of patients recovering from general anesthesia and in 30% of volunteers undergoing regional anesthesia, though an extensive data search did not reveal any new study to support this observation [25]. Shivering was observed to occur more frequently in the female gender and on use of thiopentone compared with propofol after general anesthesia [26]. Rigor occurs commonly, as a protective response to core hypothermia, though it may occur in the presence of normothermia.

Butorphanol is an opioid analgesic which has action on both µ and opioid receptors [27]. Butorphanol is agonist at receptors. The stimulation of receptors seems a likely antishivering action of butorphanol. It has not gained much popularity for routine use in treatment of shivering as very few studies regarding its use as an anti-shivering agent are available. Routinely butorphanol is used as an IV opioid analgesic, but its role in treatment of shivering is not well documented in literature.

Table 1: Basic Characteristics

Groups	Group B	Group C
Administration of	**Butorphanol**	**Clonidine**
No. of Cases	15	15
Age (years)	22 – 52	31 - 54
Sex		
Male	9	10
Female	6	5
BMI (Kg/m2)	21.1 – 23.4	20.5 – 22.8
Physical status		
ASA I	8	10
ASA II	7	5
Duration of Surgery mins	55 – 95	59 – 104

Table 2: Anti-shivering effects

Groups	Group B	Group C
Administration of	**Butorphanol**	**Clonidine**
Mean time for onset of shivering (minutes)	11 – 16	11 – 15
Time for control of shivering (seconds)	61 – 118	245 - 391
Control of Shivering: (cases)		
Complete	12	9
Incomplete	2	5
Failure	1	1
Recurrence rate (cases)	1	7
Sedation		
Present	5	8
Absent	10	7

Table 3: Side Effects

Groups	Group B	Group C
Administration of	**Butorphanol**	**Clonidine**
Itching	0	0
Nausea/Vomiting	1	2
Respiratory depression	0	0
Hypotension	0	3
Bradycardia	0	3

Clonidine is useful in the treatment of postoperative shivering. Delaunay *et al*. [28] showed that clonidine reduces the thermoregulatory threshold for both vasoconstriction and shivering and suggesting it acts by inhibiting central thermoregulatory control. It is a potent suppressor of sympathoadrenal activity [29, 31] and has been shown to blunt sympathetic response to surgical stimulation and tracheal intubation. Bradycardia and hypotension are potential adverse effects [32].

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. No similar hemodynamic effects were observed in our study [33]. 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 whereas, in our study, we observed a rise in diastolic BP and heart rate during the onset of shivering [34]. Butorphanol was quicker than pethidine in abolishing shivering successfully. Relapse is more in pethidine than butorphanol [35].

Various studies have established the role of clonidine as an antishivering agent [36, 37]. During some of the related studies, sedative effects of clonidine were noticed when a dose of 3 μg/kg was used. However, some studies revealed that even a lower dose of clonidine was effective in the reduction of shivering [38, 40]. Therefore, to minimize adverse effects, we decided to administer clonidine in a dose of 50 μg. This lower dose of clonidine used in this study was effective in the prevention of shivering but still had sedative potential.

The various treatment modalities to control shivering include pharmacological and non-pharmacological methods. The non-pharmacological methods include use of heaters, warming blankets, radiant heat, forced air warmers, infusing warm IV fluids, etc [41]. Pharmacotherapy still remains the most widely accepted method for controlling shivering because of the ease in availability of various drugs which are cheap and inexpensive. Various pharmacological interventions including pethidine, tramadol, butorphanol, clonidine, ondensetron, ketamine, doxapram, etc have been tried in control of shivering [42, 44]. As all the available drugs to control shivering have various adverse effects, still there is no single well accepted drug for control of shivering.

A constraint of this examination is that we couldn't gauge the core body temperature. For estimation of core body temperature, the test should be placed in the throat or close to the tympanic membrane. Both these are awkward and unsatisfactory who has been given spinal anesthesia. Rectal temperature checking was a probability yet was not attempted.

Conclusion

The data generated from the present study concludes that Control of shivering is faster and better with Butorphanol than Clonidine. The incidence of recurrence is significantly less with Butorphanol than Clonidine. The incidence of hemodynamic variations (bradycardia / hypotension) is significantly higher with Clonidine as compared to Butorphanol.

References

1. Corning JL. Spinal anesthesia and local medications of the cord. N Y Med J, 1885; 42:483.
2. Norris MC, Fogel ST, Conway-Long C. Combined spinal-epidural versus epidural labor analgesia. Anesthesiology. 2001; 95(4):913-20.
3. Braga Ade F, Frias JA, Braga FS, Pereira RI, Titotto SM. Spinal anesthesia for elective ceasarean section: use of different doses of hyperbaric bupivacaine associated with morphine and clonidine. Acta Cir Bras. 2013; 28(1):26-32.
4. Hoyle J, Yentis SM. Assessing the height of block for caesarean section over the past three decades: trends from the literature. Anaesthesia. 2015; 70(4):421-8.
5. Perlas A, Chan VW. Neuraxial anesthesia and multiple sclerosis. Can J Anaesth. 2005; 52(5):454-8.
6. Chattopadhyay A, Maitra S, Sen S, Bhattacharjee S, Layek A, Pal S, *et al*. A study to compare the analgesic efficacy of intrathecal bupivacaine alone with intrathecal bupivacaine midazolam combination in patients undergoing elective infraumbilical surgery. Anesthesiol Res Pract. 2013. 2013:567134.
7. Hampl K, Steinfeldt T, Wulf H. Spinal anesthesia revisited: toxicity of new and old drugs and compounds. Curr Opin Anaesthesiol. 2014; 27(5):549-55.
8. Freedman JM, Li DK, Drasner K, Jaskela MC, Larsen B, Wi S. Transient neurologic symptoms after spinal anesthesia: an epidemiologic study of 1,863 patients. Anesthesiology. 1998; 89(3):633-41.
9. Staikou C, Paraskeva A. The effects of intrathecal and systemic adjuvants on subarachnoid block. Minerva Anestesiol, 2013.
10. Rooke GA, Freund PR, Jacobson AF. Hemodynamic response and change in organ blood volume during spinal anesthesia in elderly men with cardiac disease. Anesth Analg. 1997; 85(1):99-105.
11. Liu SS, McDonald SB. Current issues in spinal anesthesia. Anesthesiology. 2001; 94(5):888-906.
12. El-Hakeem EE, Kaki AM, Almazrooa AA, Al-Mansouri NM, Alhashemi JA. Effects of sitting up for five minutes versus immediately lying down after spinal anesthesia for Cesarean delivery on fluid and ephedrine requirement; a randomized trial. Can J Anaesth. 2011; 58(12):1083-1089.
13. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology. 1992; 76(6):906-16.
14. Ben-David B, Vaida S, Gaitini L. The influence of high spinal anesthesia on sensitivity to midazolam sedation. Anesth Analg. 1995; 81(3):525-8.
15. Gabrielli A, O'Connor, Maccioli G. Anesthesia Advanced Cardiac Life Support. American Society of

Anesthesiologists, 2008. www.asahq.org/. Available at http://www.asahq.org/. Accessed: August 4, 2011.
16. Safa-Tisseront V, Thormann F, Malassiné P, *et al*. Effectiveness of epidural blood patch in the management of post-dural puncture headache. Anesthesiology. 2001; 95(2):334-9.
17. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, *et al*. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med. 2010; 35(1):64-101.
18. Zaric D, Christiansen C, Pace NL, Punjasawadwong Y. Transient neurologic symptoms after spinal anesthesia with lidocaine versus other local anesthetics: a systematic review of randomized, controlled trials. Anesth Analg. 2005; 100(6):1811-6.
19. Buggy DJ, Crossley AW. Thermoregulation, mild perioperative hypothermia and post-anaesthetic shivering. Br J Anaesth. 2000; 84(5):615-28.
20. Kurz A, Sessler DI, Schroeder M, Kurz M. Thermoregulatory response thresholds during spinal anesthesia. Anesth Analg. 1993; 77(4):721-26.
21. Leslie K, Sessler DI. Reduction in the shivering threshold is proportional to spinal block height. Anesthesiology. 1996; 84(6):1327-31.
22. Buggy DJ, Crossley AW. Thermoregulation, mild perioperative hypothermia and post-anaesthetic shivering. Br J Anaesth. 2000; 84(5):615-28.
23. Anesthesia and postoperative shivering: its etiology, treatment and prevention. Zhang Y, Wong KC Acta Anaesthesiol Sin. 1999; 37(3):115-20.
24. Shivering during epidural anesthesia. Sessler DI, Ponte J Anesthesiology. 1990; 72(5):816-21.
25. Efficacy of prophylactic ketamine in preventing postoperative shivering. Dal D, Kose A, Honca M, Akinci SB, Basgul E, Aypar U Br J Anaesth. 2005; 95(2):189-92.
26. A comparison of thiopentone and propofol with respect to the incidence of postoperative shivering. Singh P, Harwood R, Cartwright DP, Crossley AW Anaesthesia. 1994; 49(11):996-8.
27. Joshi SS, Arora A, George A, Shidhaye RV. Comparison of intravenous butorphanol, ondansetron and tramadol for shivering during regional anesthesia: Aprospective randomized double-blind study.
28. Delaunay L, Bonnet F, Liu N, Beydon L, Catoire P, Sessler DI. Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans. Anesthesiology, 1993; 79:470-4.
29. Powell RM, Buggy DJ. Ondansetron given before induction of anesthesia reduces shivering after general anesthesia. Anesth Analg, 2000; 90:1423-7.
30. Joris J, Banache M, Bonnet F, Sessler DI, Lamy M. Clonidine and ketanserin both are effective treatment for postanesthetic shivering. Anesthesiology, 1993; 79:532-9.
31. Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. Anesthesiology, 1991; 74:581-605.
32. Pouttu J, Scheinin B, Rosenberg PH, Viinamäki O, Scheinin M. Oral premedication with clonidine: Effects on stress responses during general anaesthesia. Acta Anaesthesiol Scand, 1987; 31:730-4.
33. 8. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post-spinal anaesthesia shivering. Indian J Anaesth, 2011; 55:242-6.
34. Joshi SS, Arora A, George A, Vinayak SR. Comparison of intravenous butorphanol, ondansetron and tramadol for control of shivering during regional anesthesia: A prospective, randomized double-blind study. Anaesth Pain Intensive Care, 2013; 17:33-9.
35. Saini S, Mullick P. A comparative evaluation of butorphanol with pethidine for treatment of postspinal shivering. Innov J Med Health Sci. 2014; 4:86-9.
36. Piper SN, Maleck WH, Boldt J, Suttner SW, Schmidt CC, Reich DG, *et al*. A comparison of urapidil, clonidine, meperidine and placebo in preventing postanesthetic shivering. Anesth Analg, 2000; 90:954-7.
37. Piper SN, Suttner SW, Schmidt CC, Maleck WH, Kumle B, Boldt J, *et al*. Nefopam and clonidine in the prevention of postanaesthetic shivering. Anaesthesia, 1999; 54:695-9.
38. Sia S. I.v. clonidine prevents post-extradural shivering. Br J Anaesth, 1998; 81:145-6.
39. Buggy D, Higgins P, Moran C, O'Donovan F, McCarroll M. Clonidine at induction reduces shivering after general anaesthesia. Can J Anaesth, 1997; 44:263-7.
40. Launo C, Palermo S, Germi MR, Lanfrit C, Frascà A, Simonetti F. Clonidine and postoperative shivering. Minerva Anestesiol, 1991; 57:427-31.
41. Camus Y, Delva E, Cohen S, Lienhart A. The effects of warming intravenous fluids on intra-operative hypothermia and postoperative shivering during prolonged abdominal surgery. Acta Anaesthesiol Scand. 1996; 40(7):79-82.
42. Kranke P, Eberhart LH, Roewer N, Tramer MR. Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. Anesth Analg. 2002; 94(2):453-60.
43. Wason R, Jain N, Gupta P, Gogia AR. Randomized double blind comparison of prophylactic ketamine, clonidine and tramadol for the control of shivering under neuraxial anaesthesia. Indian J Anaesth. 2012; 56(4):370-5.
44. Bhatnagar S, Saxena A, Kannan TR, Punj J, Panigrahi M, Mishra S, *et al*. Tramadol for postoperative shivering: a double blind comparison with pethedine. Anaesth Intensive care. 2001; 29(2):149-54.