

A PROSPECTIVE RANDOMISED COMPARATIVE STUDY OF 0.5% HEAVY BUPIVACAINE 15mg WITH 0.9% SALINE AND 0.5% HEAVY BUPIVACAINE 15mg WITH 2mg MIDAZOLAM INTRATHECALLY IN LOWER ABDOMINAL SURGERIES AND LOWER LIMB SURGERIES.

Dr. S. Farooq Basha ¹

Assistant Professor, Department of Anaesthesiology, ACSR government Medical College, Nellore,
Andhra Pradesh, India.

Corresponding Author: Dr. S. Farooq Basha, Flat No: 403, Teaching Staff Quarters, ACSR Government
Medical College Campus, Nellore - 524 004, Andhra Pradesh, India.

ABSTRACT:

Spinal anaesthesia is unparalleled in the way a small mass of drug, virtually devoid of systemic pharmacologic effect, can produce profound, reproducible surgical anaesthesia. Further, by altering the small mass of drug, very different types of spinal anaesthetics can be produced. Low spinal anaesthesia, a block below T10, carries a different physiologic impact than does a block performed to produce higher spinal anaesthesia (greater than T5). The block is unexcelled for lower abdominal or lower extremity surgical procedures. The main reasons for the popularity of spinal block are that the block has well-defined endpoints and the anaesthesiologist can produce the blocks reliably with a single injection⁶⁰. The versatility of spinal anaesthesia is afforded by a wide range of local anaesthetics and additives that allow control over the level, the time of onset and the duration of spinal anaesthesia. The distribution of local anaesthetic solutions within the subarachnoid space determines the extent of the neuraxial blockade produced by spinal anaesthesia. Spinal anaesthesia with hyperbaric bupivacaine 0.5% is a popular method. Addition of opioids to local anaesthetics is very commonly practised. Though the opioids reduce the toxicity and cardiovascular effects of local anaesthetics this type of combinations may bring about additional undesirable problems like itching, nausea and vomiting and/or respiratory depression. Instead, there are many clinical studies in favour of intrathecal midazolam which has added advantages since it produces sedation, amnesia and anti nociceptive effects without any neurotoxicity or other side effects. Hence this study was designed to evaluate the efficacy, to know the duration of pain relief and to know the incidence of adverse effects and complications when midazolam is given along with bupivacaine intrathecally.

I. AIMS AND OBJECTIVES

- 1) To determine the clinical advantages of sub-arachnoid administration of Midazolam to qualitative regional blocks with Bupivacaine with regard to the provision of adequate intra-operative analgesia in lower limb and lower abdominal surgeries.
- 2) To assess the analgesic effect, sedation and to note the enhancement of post operative analgesia by the use of a benzodiazepine like Midazolam as an adjuvant to local anaesthetic — 0.5% hyper baric Bupivacaine.
- 3) To study the other added benefits of using Midazolam as an adjuvant.

II. MATERIALS AND METHODS:

A clinical study comparing the effect of the addition of Midazolam to Bupivacaine to increase the analgesic effects of the spinal blockade in patients undergoing lower abdominal and lower limb surgeries done in the Department of Anaesthesiology at ACSR Government Medical College, Nellore. The study was undertaken after obtaining Hospital Ethics Committee clearance as well as written, informed consent from all patients after explaining and reassuring about the spinal procedure. A hundred patients posted for various elective lower limb and lower abdominal surgeries were studied in a randomized prospective manner.

Inclusion criteria

1. Patients between the age 18–55 years of both sexes.
2. Patients belonging to American Society of Anesthesiologists physical status I/II.
3. Patients posted for elective lower limb and lower abdominal surgeries.

Exclusion Criteria

Patients with a history of known sensitivity to the drugs used. Patients with gross spinal deformity, peripheral neuropathy or had any contraindication to neuraxial block - local / Systemic infections, coagulation disorders, hypovolemia, signs of raised intracranial tension, uncontrolled hypertension.

III. RESULTS AND CONCLUSION:

In this present study, we compared 0.5% hyperbaric bupivacaine 15mg and 0.5% hyperbaric bupivacaine 15mg with 2mg midazolam given intrathecally. The present study was conducted on 100 patients of either sex in the age group between 18-60 years belonging to ASA Grade I and II. These patients were posted for elective lower abdominal and lower limb surgeries.

The patients were divided into two groups of fifty each.

Group I received 0.5% hyperbaric bupivacaine 3ml+0.4ml 0.9% normal saline.

Group II - received 0.5% hyperbaric bupivacaine 3ml + 0.4ml preservative free Midazolam (2mg)

With the present study, we can summarize the usage of preservative-free midazolam in the subarachnoid block as an additive with bupivacaine provides faster onset of sensory and motor block, better sedation. good quality and prolonged post operative analgesia with minimal side effects.

IV. DISCUSSION:

Pre-anaesthetic Evaluation

A thorough pre-anaesthetic evaluation with general physical and systemic examination was done the evening before the proposed surgery. General examination included recording pulse rate, blood pressure, airway assessment, examination of the respiratory and cardiovascular systems, spinal deformities and local infection at the lumbar puncture site.

Technique

A lumbar subarachnoid block was performed under strict aseptic precautions with the patient in the right lateral position with a pillow under the head and the table flat or, in the sitting position, when the patient could not be placed in the lateral position. Lumbar tap was made in the L3-4 inter-space, midline approach, using 23 Gauge Quincke needle, after local infiltration of skin using 2% Xylocaine. After obtaining a clear flow of CSF, the drug was injected slowly, after negative aspiration for blood. 0.4ml of Midazolam and 0.4 ml of 0.9% normal saline were measured using Insulin syringe.

Patients were made to lie supine immediately after the completion of the injection. The time of injection of the drug was recorded as 0 minutes. During surgery, all patients were given intravenous fluids-Isotonic saline and ringers lactate for maintenance.

Intra operative Monitoring

NIBP, ECG, Pulse Oximeter were the intraoperative monitors used. The Heart rate and SpO₂ were monitored continuously. Blood pressure was recorded every 2 minutes for the first 20 minutes, every 5 minutes for the rest of the operation. Time intervals at which hypotension, bradycardia or other complications occurred were noted. Oxygen 4L/min via face mask was administered to all patients through out the procedure. Respiratory rate was monitored. Sedation score was recorded every 10 minutes the first hour and every 30 minutes next till end of surgery.

Parameters studied

The following parameters were studied

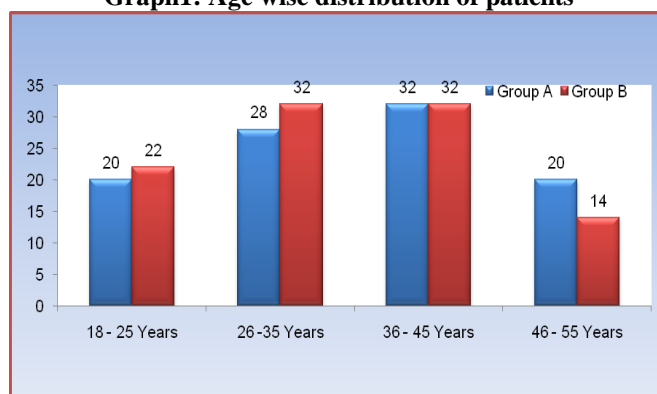
- 1) Assessment of sensory blockade: Sensory blockade was assessed by pinprick and time noted for the block to reach different dermatomal level.
 - a) The onset of sensory block
 - b) Maximum height reached
 - c) Duration of analgesia
- 2) Assessment of onset of motor blockade.
- 3) The patients were carefully monitored for any untoward effects like inadequate block, hypotension, bradycardia, respiratory distress, nausea, vomiting, restlessness, pruritis, shivering, anaphylactic reaction intraoperatively.

Patients were shifted to the postoperative ward and observed till the first administration of analgesic (Diclofenac sodium 1.5mg/kg, intramuscularly was given when the patient demanded it) and for the next 72 hours postoperatively.

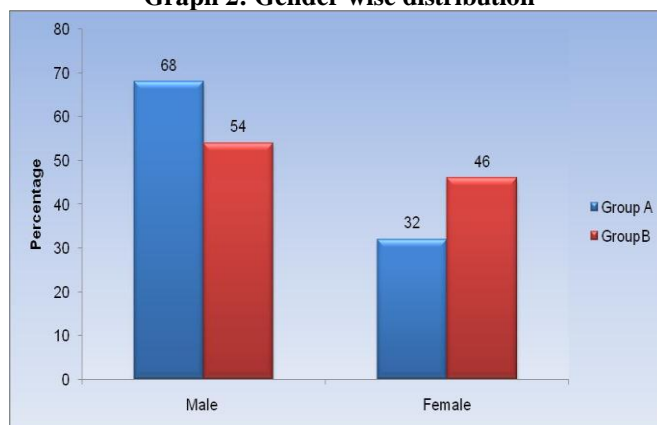
V. RESULTS

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean \pm SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Paired t test is used to find the significance of study parameters between two groups of patients and chi-square test has been used to find the significance of study parameters on categorical scale between two groups. Statistical software spss 20.0 were used for the analysis of the data and Microsoft word and excel have been to generate graphs, tables etc. The results and interpretations are explained below.

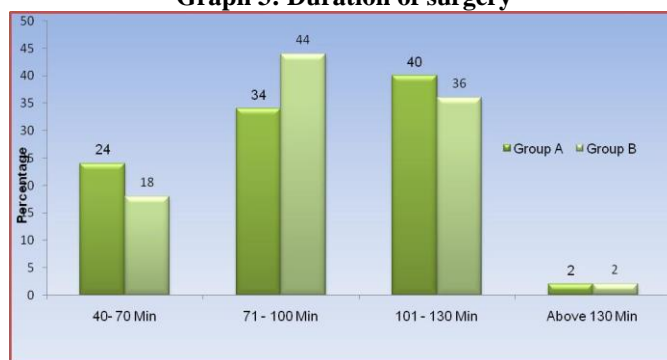
Graph1: Age wise distribution of patients



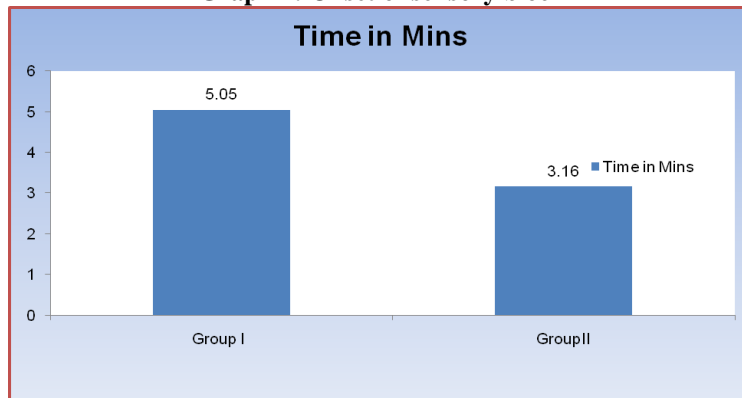
Graph 2: Gender wise distribution



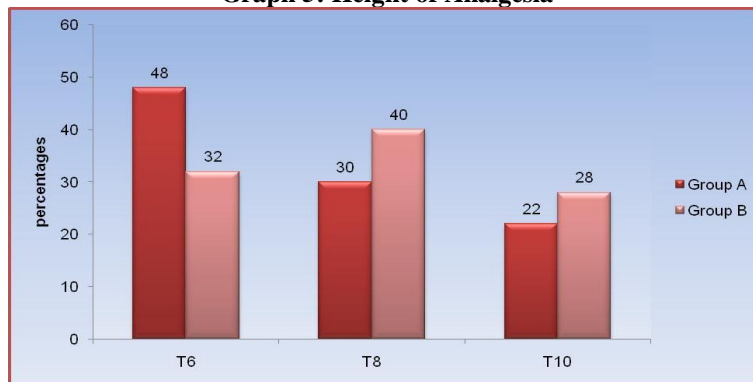
Graph 3: Duration of surgery



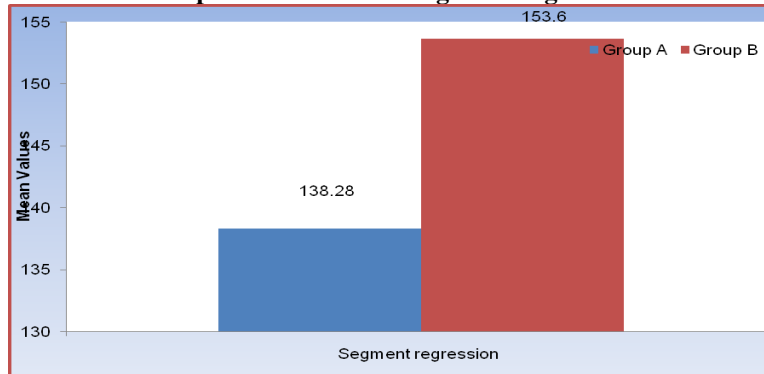
Graph 4: Onset of sensory block



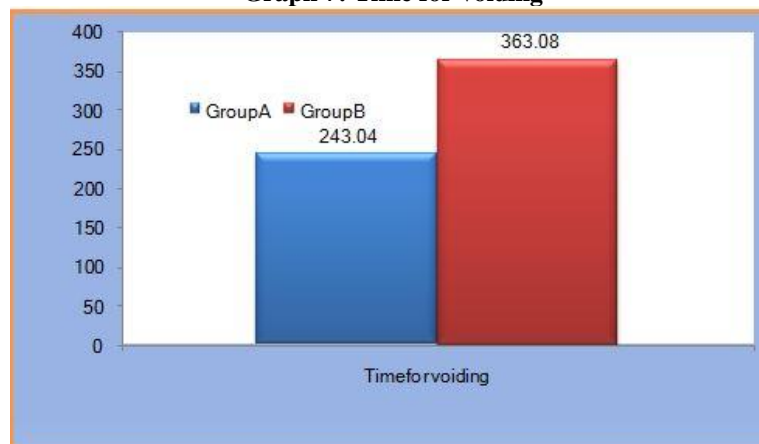
Graph 5: Height of Analgesia



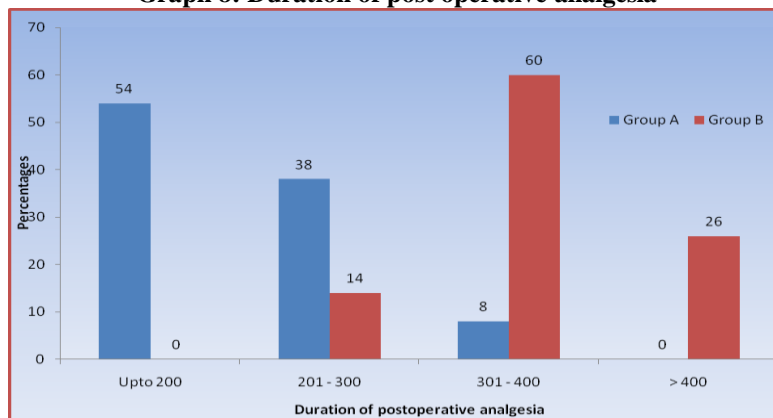
Graph 6: Time for two Segment Regression



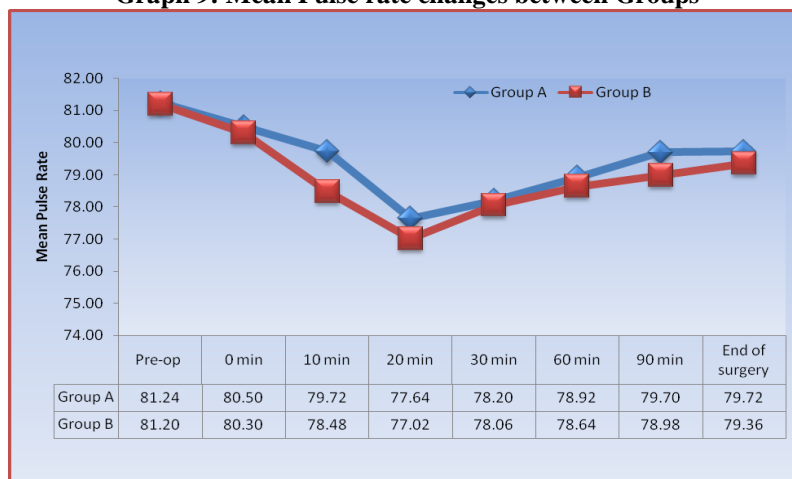
Graph 7: Time for voiding



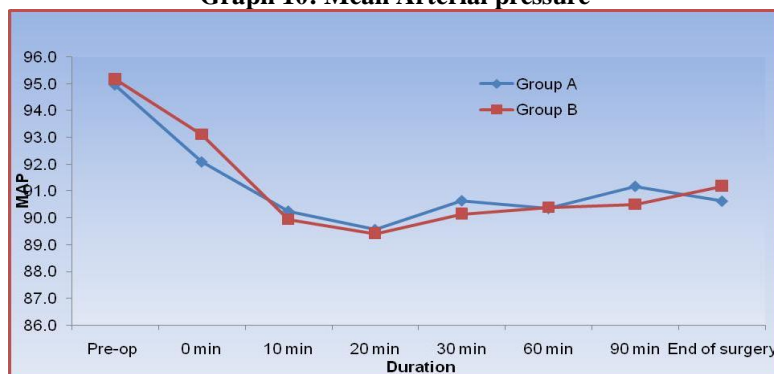
Graph 8: Duration of post operative analgesia



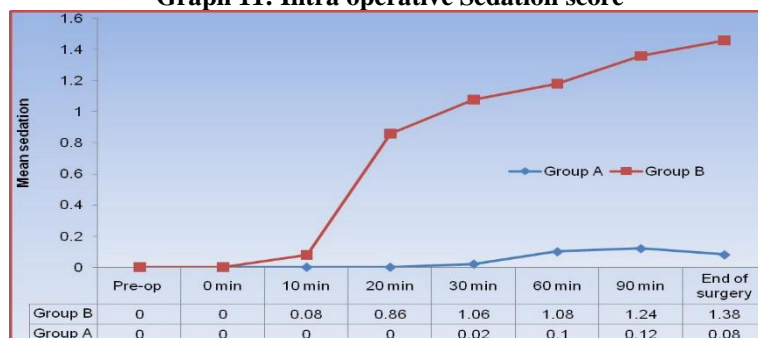
Graph 9: Mean Pulse rate changes between Groups



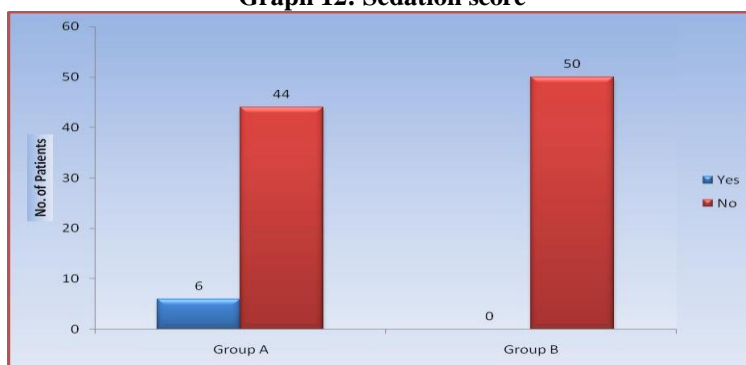
Graph 10: Mean Arterial pressure



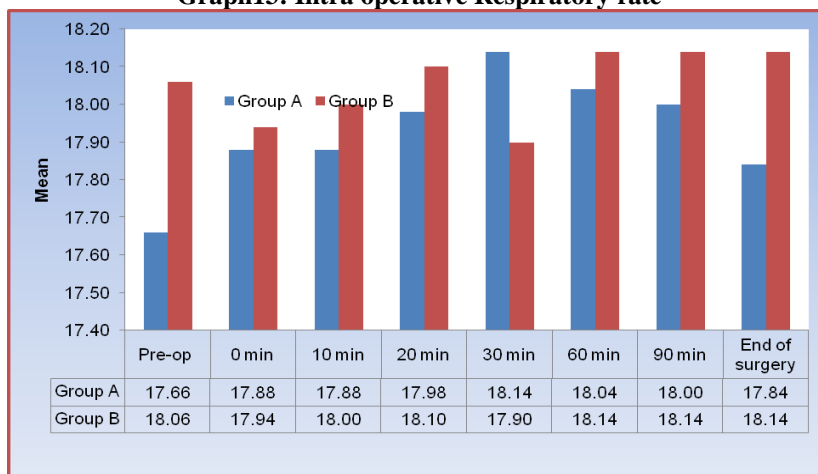
Graph 11: Intra operative Sedation score



Graph 12: Sedation score



Graph13: Intra operative Respiratory rate



Results of the present study

In this study, the patients across the group did not vary much with respect to age, sex, height. In both groups, all the parameters were kept identical to avoid intraoperative and postoperative variations. In both groups, surgeries performed were almost identical.

Results of the present study

	GroupI	GroupII
Mean age (years)	35.48±10.63	34.40±9.99
Mean duration of surgery (mins)	94.10±25.69	95.88±21.97
Mean Onset of sensory block (mins)	5.05±0.79	3.16±0.53
Mean Onset of the motor blockade (mins)	5.24±0.80	3.44±0.54
Mean time for two segment regression (mins)	138.28±18.39	153.6±20.83
Mean time of postoperative analgesia (mins)	214.60±43.63	360.86±56.21
Mean time for Voiding (mins)	243.03±49.76	363.08±49.79
Hypotension%	2	2
Bradycardia%	3	2
Shivering%	3	2
Nausea+shivering%	2	1
H+B%	2	1

VI. CONCLUSION

On the basis of Anatomy, Neurophysiology, pathophysiology, pharmacology and the development of more effective techniques for the effective management of intraoperative analgesia, most of the patients suffer from pain in the postoperative period. It is proven that relief of pain with a subarachnoid block with a local

anaesthetic like Bupivacaine alone, is limited to the initial postoperative period. When a combination of bupivacaine and an adjuvant-like Midazolam is used, pain relief can be extended well into the postoperative period.

On the basis of this study, the conclusion is

1. Midazolam added with bupivacaine shows the faster onset of both sensory and motor block than bupivacaine alone.
2. The superior quality of surgical anaesthesia.
3. Intraoperative sedation is adequate with an addition of intrathecal midazolam, decreases the additional supplementation of sedatives
4. Good hemodynamically stability.
5. The postoperative analgesic requirement is decreased by prolonging the duration of analgesia.
6. Minimal side effects.

VII. SUMMARY

The subarachnoid blockade is effective in the management of both intraoperative pain and initial postoperative period. In order to increase the duration of postoperative pain, decrease intraoperative and postoperative complications, decrease postoperative supplementations many drugs are used as additives in the spinal block.

In this present study, we compared 0.5% hyperbaric bupivacaine 15mg and 0.5% hyperbaric bupivacaine 15mg with 2mg midazolam given intrathecally.

The present study was conducted on 100 patients of either sex in the age group between 18-60 years belonging to ASA Grade I and II. These patients were posted for elective lower abdominal and lower limb surgeries.

The patients were divided into two groups of fifty each.

Group I-received 0.5% hyperbaric bupivacaine 3ml+0.4ml 0.9% normal saline.

Group II - received 0.5% hyperbaric bupivacaine 3ml + 0.4ml preservative free Midazolam (2mg).

The following parameters were compared between the 2 groups.

1. Time of onset of sensory block.
 2. The maximum level of blockade.
 3. Duration of sensory block.
 4. The onset of motor blockade.
 5. Duration of analgesia.
 6. Time of first voiding as a measure of sympathetic recovery.
 7. The incidence of the complications was also compared between two groups.
 8. The present study across the group did not vary much with respect to age, sex, and duration of surgery.
- The onset of the sensory blockade and motor blockade was faster with the addition of midazolam to bupivacaine as compared to bupivacaine. The mean time of two segment regression, mean time of voiding is prolonged in Midazolam group as compared to Group I, The mean time of postoperative analgesia was significantly prolonged with the addition of 2mg midazolam to bupivacaine.

All patients in Group II were sedated and calm throughout the procedure and required no supplementation whereas 12% of Group I patients required sedation. Patients were observed intraoperatively and postoperatively for 72 hours and assessed for occurrence of complications like hypotension, bradycardia, nausea, shivering, and delayed complication like urinary retention, Transient neurological symptoms, post-dural puncture headache, stable in both groups.

With the present study, we can summarize the usage of preservative-free midazolam in the subarachnoid block as an additive with bupivacaine provides faster onset of sensory and motor block, better sedation, good quality and prolonged post operative analgesia with minimal side effects.

REFERENCES

- [1]. Maged L. Boules, Joseph M. Botros: Intrathecal midazolam versus intrathecal midazolam plus magnesium sulfate for analgesia in cesarean section Boules and Botros. *Ain-Shams Journal of Anesthesiology*-2015;8:70-75.
- [2]. Premalatha S, Sureshu P. Comparative study of hyperbaric bupivacaine and bupivacaine with midazolam in subarachnoid block for postoperative analgesia in perianal surgeries. *Int J Res Health Sci [Internet]*. 2014 Jan 31;2(1):162-5.
- [3]. I Punjabi, Waqar-ul-Nisa, A Farooqi, A Ahmad, A Maqbool. Effect Of Intrathecal Midazolam On Quality And Duration Of Spinal Anesthesia With Bupivacaine In Perineal And Lower Limb Surgery. *The Internet Journal of Anesthesiology*. 2013 Volume 32 Number 1.
- [4]. Sanwal MK, Baduni N, Jain A. Bupivacaine sparing effect of intrathecal midazolam in sub-arachnoid block for cesarean section. *J Obstet Anaesth Crit Care* 2013;3:27-31
- [5]. Shashni S, Nair AS, Gopal IT. Clinical effects of intrathecal midazolam versus intrathecal magnesium sulfate as adjuncts to

- hyperbaric bupivacaine: A comparative study. Indian J Pain 2013;27:175-81.
- [6]. Anirbanchattopadhyay, Souvikmaitra, Suvadeepsen "midazolam in subarachnoid: current evidence" ISRN Anesthesiology volume 2013 (2013) Article ID 202835, 7 pages, 293.
- [7]. A Karbasfrushan, K Farhadi, J Amiri-Saman, S Bazargan-Hejazi, A Ahmadi: Effect of Intrathecal Midazolam in the Severity of Pain in Cesarean Section: A Randomized Controlled Trial/Iran Red Crescent Med J 2012; 14(5):276- 282.
- [8]. Anjali Bhure, Neelakshi Kalita, Prasad Ingle, C.P. Gadkari: Comparative study of intrathecal hyperbaric Bupivacaine with Clonidine, Fentanyl and Midazolam for quality of anaesthesia and duration of postoperative pain relief in patients undergoing elective caesarean section/People's Journal of Scientific Research/ Vol. 5(1)/Jan. 2012.,19-23.
- [9]. Joshi SA, Khadke VV, Subhedar RD, Patil AW, Motghare VM. Comparative evaluation of intrathecal midazolam and low dose clonidine: Efficacy, safety and duration of analgesia. A randomized, double blind, prospective clinical trial. Indian J Pharmacol 2012;44:357-61.
- [10]. AbdulMuthalib Hussain, Badurudeen, Mahmood Buhary; Zikrullah Tamanna- Comparative Study of Intrathecal Midazolam and Ketamine with Bupivacaine for Post-Operative Analgesia in the lower limb and perianal surgeries/Biomedical Research 2012(2): 259-267.
- [11]. Indrajit Kumar, Shashiprakash, R K Verma, Sandeepkhuba, A K Paswan, U S Dwivedi- analgesic efficacy of intrathecal midazolam with bupivacaine in patients undergoing transurethral resection of prostate/Asian journal of modern and ayurvedic medical science/(ISSN 2279-0772) July 2012, vol.1 no.1.
- [12]. Shadangi BK, Garg R, Pandey R, Das T- Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomised case control study/Singapore medical journal 2011 June,56(6):432-5.
- [13]. Brown DL. Spinal, epidural and caudal anaesthesia. 7th ed. Chapter 51. In: Miller's Anesthesia, Miller RD, ed. Philadelphia: Elsevier Churchill Livingstone; 2010. pp. 1613-16.
- [14]. Brown DL. Spinal, epidural and caudal anaesthesia. 7th ed. Chapter 51. In: Miller's Anesthesia, Miller RD, ed. Philadelphia: Elsevier Churchill Livingstone; 2010. pp. 1625.
- [15]. Bernardis CM Epidural and spinal anaesthesia. 6th ed. Chapter 37. In: Clinical Anaesthesia, Barash PG, Cullin BF, Stoelting RK, eds. Philadelphia: Lippincott Williams & Wilkins. 2009; pp. 928-37.
- [16]. Mc Graw Hill. NYSORA. Textbook of Regional Anesthesia and Acute Pain Management by Admir Hadzic. 2007 ed Part III; pp. 216-21.
- [17]. Dr. komal Study Of Postoperative Pain Relief In Cesarean Section With Intrathecal Midazolam. (A Study Of 50 Cases)./International Journal of Anesthesia/ISSN 1361-8245.
- [18]. N Agarwal, A Usmani, R Sehgal, R Kumar, P Bhadoria. Effect of intrathecal midazolam bupivacaine combination on postoperative analgesia. Ind J Anaesth 2005; 49(1): 39-39.
- [19]. Brown DL: Spinal, Epidural, Caudal anaesthesia. In Miller RD (ed): Anesthesia, 6th ed. Churchill Livingstone, 2005, pp 1657.
- [20]. Hocking G, Wildsmith JAW. Intrathecal Drug Spread. Br J Anaesth 2004;93(4) : 568-78.
- [21]. Tucker PA, Lai C, Nadeson R, Goodchild CS. Intrathecal Midazolam II: A cohort study investigating safety. Anesth Analg 2004; 98: 1512-1520.
- [22]. Shah FR, Halbe AR, Panchal ID, Goodchild CS. Improvement in postoperative pain relief by the addition of Midazolam to an intrathecal injection of buprenorphine and bupivacaine. Eur J Anaesthesiol 2003;20(11): 904-910.
- [23]. Bhattacharya D, Biswas B, Banerjee A. Intrathecal midazolam with bupivacaine increases the analgesic effects of spinal blockade after major gynaecological surgery. J Anaesth Clin Pharmacol 2002; 18(2): 183-186.
- [24]. Bharti N, Madan R, Mohanty PR, Kaul HL. Intrathecal Midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia. Acta Anaesth Scand 2002; 47(9): 1101-1105.
- [25]. Vaswani RK, Raiger LK, Purohit R, Bajaj P. The effect of intrathecal midazolam on postoperative pain relief in orthopaedic surgery. Hospital Today 2002; 7(4):150-153.
- [26]. Larson MD. History of anaesthetic practice, Chapter 1 in Miller's Anesthesia, Sixth Edition, Elsevier Churchill Livingstone, 2004; 3-54.
- [27]. Yaksh TL, Allen JW. The use of intrathecal midazolam in humans: a case study of the process. Anesth Analg 2004; 98: 1536-1545.
- [28]. Sen A, Rudra A, Sarkar SK, Biswas B. Intrathecal Midazolam for postoperative pain relief in caesarean section delivery. J Indian Med Assoc 2001; 99(12): 683-686.
- [29]. Kim MH, Lee YM. Intrathecal Midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. Br J Anaesth 2001; 86: 77-79.
- [30]. Miller Ronald D. Local Anesthetics in: Anesthesia, 5th Edition, Vol. 1 Philadelphia, Churchill Livingstone, 2000.
- [31]. Batra YK, Jain K, Chari P, Dhillion MS, Shaheen B, Reddy GM. Addition of intrathecal midazolam to bupivacaine produces better postoperative analgesia without prolonging recovery. Int J Clin Pharmacol Ther 1999; 37(10): 519-523.
- [32]. Nishiyama Y, Hanaoka K. Midazolam can potentiate the analgesic effects of intrathecal bupivacaine on thermal or inflammatory induced pain. Anesth Analg 2003; 96: 1386-1391.
- [33]. Nishiyama T, Sugai N, Hanaoka K. In-vitro changes in the transparency and Ph of CSF caused by adding midazolam. Eur J Anaesthesiol 1998;15(1): 27- 31.
- [34]. Nishiyama T, Yokoyama L, Hanaoka I. Midazolam improves postoperative epidural analgesia with continuous infusion of local anaesthetics Anaesthesiology 1998; 45(6): 551-555.
- [35]. Nishiyama T, Matsukawa T, Hanaoka K. Acute phase histopathological study of spinally administered midazolam in cats. Anesth Analg 1999; 89: 717.
- [36]. Valentine JM, Lyons G, Bellamy MC. The effect of intrathecal Midazolam on postoperative pain. Eur J Anaesthesiol 1996; 13(6): 589-93.
- [37]. Borg PAJ, Krijnen HJ. Long-term intrathecal administration of Midazolam and clonidine. The Clinical Journal of Pain 1996; 12(1): 63-68.
- [38]. Naguib M, El Gammal M, El Hattab YS, Seraj M. Midazolam for caudal analgesia in children - Comparison with caudal Bupivacaine. Can J Anaesth 1995; 42(9): 758-764.
- [39]. Serrao JM, Marks RL, Morley SJ, Goodchild CS. Intrathecal Midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. Pain 1992; 48(1): 5-12.
- [40]. Nishiyama T, Okada Y, Hirasaki A, Mikane T, Kobayashi O, Seto K. Epidural midazolam with bupivacaine—optimal dose for postoperative pain relief. Masui 1992; 41(7): 1113 –1118.
- [41]. Goodchild CS, Serrao JM. Intrathecal Midazolam in the rat—evidence for spinally mediated analgesia. Br J Anaesth 1987; 59: 1563-70.
- [42]. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man—

- apilotstudy.BrJClinPharmacol1987; 23: 279-285.
- [43]. Goodchild CS, Guo Z, Musgrave A, Gent JP. Antinociception by intrathecal Midazolam involves endogenous neurotransmitters acting at spinal cord δ opioid receptors. *Br J Anaesth* 1996; 77: 758-763.
- [44]. Crawford ME, Jensen FM, Toftdahl DB, Madsen JB. Direct spinal effect of intrathecal and extradural midazolam on visceral noxious stimulation in rabbits. *Br J Anaesth* 1993; 70: 642-646.
- [45]. Valentine JM, Lyons G, Bellamy MC. The effect of intrathecal Midazolam on postoperative pain. *Eur J Anaesthesiol* 1996; 13(6): 589-93.
- [46]. Cousins MJ, Bridenbaugh PO. Spinal neural blockade in Neural Blockade. In *Clinical Anesthesia and Management of Pain*. 3rd Edition, Philadelphia, Lippincott-Raven, 1998.
- [47]. Collins VJ. Spinal anaesthesia. In: *Principles of Anesthesiology—General & Regional Anesthesia*, 3rd Edition, Philadelphia, Lea and Febiger, 1993 pp- 1444-45.
- [48]. Collins VJ. Spinal Analgesia-Physiologic effects. 3rd ed. In: *Principles of Anaesthesia: General and Regional Anesthesia*. Philadelphia: Lea A Febriger; 1993. pp. Def-pp-1445.
- [49]. H.Ellis, S Feldman, W.Harrop-Griffiths, *Anatomy for anaesthetists.*, 8th ed, Part 3, vertebral canal and its contents.
- [50]. Lee JA, Atkinson RS, Watt MJ. Cerebrospinal Fluid. Chapter 3 in Sir Robert Macintosh's *Lumbar Puncture and Spinal Analgesia - Intradural and extradural*, Fifth Edition, Churchill Livingstone, 1985: 88-97.
- [51]. Lee JA, Atkinson RS, Watt MJ. Physiology of Central Neuraxial Blockade, Chapter 4 in Sir Robert Macintosh's *Lumbar Puncture and Spinal Analgesia - Intradural and extradural*, Fifth Edition, Churchill Livingstone, 1985: 93-117.
- [52]. Greene NM: Distribution of local anaesthetic solutions within the subarachnoid space, *Anesth Analg*. 1985;64:715-30.
- [53]. VJ Collins. Spinal Analgesia-Physiologic effects. 3rd ed. In: *Principles of Anaesthesia: General and Regional Anesthesia*. Philadelphia: Lea A Febriger; 1993. pp. 1499-516; pp. 1208-16.
- [54]. VJ Collins. Spinal Analgesia-Physiologic effects. 3rd ed. In: *Principles of Anaesthesia: General and Regional Anesthesia*. Philadelphia: Lea A Febriger; 1993. pp. 1555-68.
- [55]. Morgan GE Jr, Mikhail MS, Murray MJ. Pain management. 4th ed. In: *Clinical Anaesthesiology*. New York: Tata McGraw-Hill; 2009. pp. 361-8.
- [56]. VJ Collins. Mechanisms of pain and control. 3rd ed. In: *Principles of Anaesthesia: General and Regional Anesthesia*. Philadelphia: Lea A Febriger; 1993. pp. 1320-41.
- [57]. Hardman JG, Limbird LE, Goodman Gillman A. Local Anesthetics in: *The Pharmacological Basis of Therapeutics*, 10th Edition, United States of America, McGraw Hill, 2001.
- [58]. Dollery C. Bupivacaine Hydrochloride, in: *Therapeutic Drugs*, 2nd Edition, Edinburgh, Churchill Livingstone, 1999.
- [59]. Stoelting RK. Local Anesthetics in: *Pharmacology & Physiology in Anaesthetic Practice*, 3rd Edition, Philadelphia, New York, Lippincott Raven, 1999.
- [60]. Brown DL. Spinal block in *Atlas of Regional Anesthesia*, 2nd Edition, Philadelphia, WB Saunders Company, 1999.
- [61]. Serrao JM, Stubbs SC, Goodchild CS, Gent JP. Intrathecal midazolam and fentanyl in the rat: evidence for different spinal antinociceptive effects. *Anesthesiology* 1989; 70: 780-786.
- [62]. Dennis S Charney, John S Mihit and Adron R Harris. Hypnotics and sedatives. Chapter 17 in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, Tenth edition, McGraw Hill, 399-427.
- [63]. Lin D, Becker K, Shapiro HM. Neurologic changes following epidural injection of Potassium chloride and Diazepam: A case report with laboratory correlations. *Anesthesiology* 1986; 65: 210-212.
- [64]. Niv D, Whitwam JG, Loh L. Depression of nociceptive sympathetic reflexes by the intrathecal administration of Midazolam. *Br J Anaesth* 1983; 55: 541-546.
- [65]. Bahar M, Cohen ML, Grinshpon Y, Chanimov M. Spinal Anesthesia with Midazolam in the rat. *Can J Anaesth* 1997; 44(2): 208-215.
- [66]. Nishiyama T. The postoperative analgesic action of Midazolam following epidural administration. *Eur J Anaesthesiol* 1995; 12: 369-374.
- [67]. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: Pharmacology and Uses—Review Article. *Anesthesiology* 1985; 62: 310-24.
- [68]. Yegin A, Sanli S, Dosemeci L, Kayacan N, Akbas M, Karsli B. The analgesic and sedative effects of intrathecal midazolam in perianal surgery. *Eur J Anaesthesiol* 2004; 21(8): 658-662