Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(5) (Part - II): 1834-1839
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6519.49

Comparison of Postoperative Analgesia Following Epidural Bupivacaine and Epidural Bupivacaine with Verapamil in Orthopaedic Lower Limb Surgeries

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Abstract

Introduction: Various attempts have been made to prolong neuraxial blockade. Calcium channel blockers have shown to inhibit pain pathway. In this study verapamil was added along with local anesthetic via epidural route. *Materials and Methods:* A double-blind randomized controlled study done with 40 ASA I and II patients undergoing elective lower limb orthopedic surgery by randomly allocating them into two groups each consisting of 20 patients. Under aseptic precautions epidural catheter was placed in L2–L3 interspace in all patients. Patients belonging to Group P received 12 ml of Inj. Bupivacaine 0.25% + 2 ml of normal saline and Patients belonging to Group V received 12 ml of Inj. Bupivacaine 0.25% + 5 mg of Inj.Verapamil diluted to 2 ml. And further supplementary doses were done with 6 ml of 0.25% Bupivacaine every 60 minutes. The intraoperative and postoperative vitals were monitored and intensity of pain was measured by using the verbal rating pain scale at 2, 6, 12, 24, 48 hour intervals. *Results:* The observations were analyzed using student *t* test. The postoperative pain score (verbal rating scale) was found to be low at all time intervals (2, 6, 12, 24, and 48 hrs) in Group V when compared to Group P. Significantly low-pain scores were observed at 2, 6, 12 and 48 hours intervals in patients belonging to Group V ($p < 0.01$ at 2, 6, and 48 hours intervals and $p < 0.05$ at 12 hours interval) than Group P. *Conclusion:* Pain relief was significantly better ($p < 0.05$) in patients who received epidural bupivacaine with verapamil mixture than the patients who received epidural bupivacaine with placebo.

Keywords: Epidural; Verapamil; Additive; Calcium channel blocker.

How to cite this article:

Suresh Kumar K, Dilip Chandar D, Deepa Lakshmi *et al.* Comparison of Postoperative Analgesia Following Epidural Bupivacaine and Epidural Bupivacaine with Verapamil in Orthopaedic Lower Limb Surgeries. Indian J Anesth Analg. 2019;6(5 P-II):1834-1839.

Introduction

Neuraxial anesthesia is a technique by which the nerves around the spinal cord are blocked by instilling local anesthetics around the nerves. There are various approaches in achieving neuraxial blockade like subarachnoid blockade, epidural blockade and combined spinal-epidural techniques. Though neuraxial blockade is the widely used technique of choice for surgeries involving lower abdomen and lower limbs the biggest disadvantage is the limited duration of action.

Recently attempts have been made to prolong the action of local anesthetics in neuraxial anesthesia

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Received on 15.07.2019, **Accepted on** 16.08.2019

by adding various additives with them. Studies have shown that Calcium influx in the presynaptic membrane leads to release of neurotransmitters which are responsible for nociception and transmitting pain.[1] And by blocking calcium channels the pain pathway can be inhibited and by using calcium channel blocker concomitant to a local anesthetic can prolong the duration of local anesthetic.[2,3]

Verapamil is a dihydropiridine L-type voltage-gated calcium channel antagonist and evidence have shown that it potentiates the effect of local anesthetics by blocking calcium channels.[4,5] This study was done due to paucity of literature in the role of verapamil in neuraxial anesthesia. The aim of this study was to evaluate the analgesic efficacy of bupivacaine and verapamil mixture given through lumbar epidural route for postoperative analgesia in patients undergoing elective orthopedic lower limb surgeries.

Materials and Methods

After getting approval from institutional ethics committee the study was done on Government Stanely Hospital, Chennai, Tamil Nadu, India from a period of March 2006 to March 2008. The study design was of double-blind randomized control trial. A total of 40 patients of ASA I & II category who were admitted to undergo elective orthopedic lower limb surgeries were enrolled into the study. Patients with contraindications for epidural anesthesia and patients who did not satisfy the inclusion criteria were excluded from the study. A written informed consent was taken from all the study participants explaining the nature and possible ill effects of the study in their native language.

All the patients before enrolling to study were examined thoroughly and investigated with various routine biochemical tests, Electrocardiogram and chest X-ray to identify any preexisting life-threatening conditions. The patients were randomized into two groups namely Group P and Group V by means of computer generated numbers. All the patients were uniformly premedicated the previous night with tablet alprazolam 0.25 mg. The study drug were Injection Verapamil 5 mg diluted to 2 ml with sterile water for Group V and 2 ml of normal saline was taken as placebo drug for Group P. Before the patients were mobilized to operation theater the study drug will be loaded in a 2 ml syringe covered with black wrapper and will be handed over to the attending anesthesiologist.

On arrival in the operating room, baseline cardiorespiratory parameters, viz., Heart rate (HR), Systolic blood pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Respiratory rate (RR) were recorded. A good intravenous access was started at the non-operative side forearm of the patient using 18G IV cannula. Preloading with crystalloids (10 ml/kg) was done.

With the patient in sitting posture, after informing the procedure to the patient and under strict aseptic precautions, epidural space was identified at L2–L3 interspace using 17G Tuohy needle by Loss of Resistance technique. 19G epidural catheter was threaded in a cephalad direction and 4 cm catheter length was kept inside the epidural space. Test dose of 3 cc of 1.5% lignocaine with adrenaline (5 µg/ml) was given to check the position of catheter.

A standard anesthetic technique was followed in all patients.

Epidural 1st dose — 14 ml of 0.5% bupivacaine + 2 ml of placebo or injection verapamil.

Epidural 2nd dose — 6 ml of 0.5% bupivacaine.

Epidural 3rd dose — 6 ml of 0.25% bupivacaine.

Epidural 2nd dose was given exactly 60 minutes after the first dose and epidural 3rd dose was given exactly 60 minutes after the epidural 2nd dose. Patients with duration of surgery between 2–2:30 hours requiring standard 3 doses of epidural local anesthetics were only taken up for study. Unanticipated prolonged duration of surgery (requiring more than 3 doses) were excluded from the study.

Intraoperatively the patient was monitored with Electrocardiogram (ECG), Non-invasive blood pressure (NIBP), Pulse oximetry (SpO_2) and urine output. During the entire operative procedure, Heart rate (HR). Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), respiratory rate (RR) was continuously monitored and recorded every 5 minutes. All patients were given oxygen supplementation (4–5 L/min) through Hudson's face mask. All the patients were given anxiolytic — Injection Midazolam 0.05 mg/kg IV. No. intravenous opiod analgesics were supplemented during the study.

Intravenous fluid management was done based on mean arterial blood pressure and surgical blood loss. The intraoperative and postoperative observations were made by the attending anesthesiologist who was unaware about the nature of study drug.

Postoperative Monitoring

Postoperatively the patient was transferred to the recovery room and observed continuously for 60 minutes. Patient was then shifted to the postoperative ward where pulse rate, systolic blood pressure, diastolic blood pressure and respiratory rate were recorded at 2, 6, 12, 24, 48 hour intervals. The patients were assessed by the same observer in the postoperative period who was blinded for the group assignment. The intensity of pain was measured by using the verbal rating pain scale at 2, 6, 12, 24, 48 hour intervals.

Pain Score (Verbal Rating Scale)

Grade 0	No complaint of pain
Grade 1	Patient complaints of pain but tolerable. (Mild pain)
Grade 2	Patient complaining of severe pain and demands relief. (Moderate pain)
Grade 3	Patient restless and screaming with pain. (Severe pain)

When the patient complained of pain, i.e., the pain intensity was assessed based on Verbal Rating Scale, if the pain score reaches 1, patient was given injection diclofenac sodium 75 mg intramuscularly. The time of first rescue analgesia (TFA) was calculated from the time of injection of the study drug in the epidural space to the time when the verbal rating pain score reached 1.

Number of supplementary analgesics (Injection Diclofenac sodium 75 mg IM) required by each patient for period of 48 hours was noted in both the groups. Occurrence of significant side effects hypotension, bradycardia were noted.

Results

The observations were analyzed using Statistical Package of Social Studies Software Version 16 (SPSS 16). Qualitatve data were analyzed using chi-square test and quantitative data was analyzed using Student t test. Table 1 shows the distribution of demographic characteristics among the groups.

The intraoperative changes in hemodynamics were comparable between both the groups, there was no statistically significant differences between them, Figures 1 and 2 Show the Intraoperative heart rate and mean arterial pressure changes between the groups.

The postoperative pain score (verbal rating scale) was found to be low at all time intervals (2, 6, 12, 24, and 48 hrs) in Group V when compared to Group P. Significantly low pain scores were observed at 2, 6, 12 and 48 hours intervals in patients belonging to Group V ($p < 0.01$ at 2, 6, and 48 hours intervals and $p < 0.05$ at 12 hours interval) than Group P as shown in Table 2.

Table 1: Demographic Characteristics Among Groups

S. No.	Parameters	Group		*p* value
		Group P Mean ± SD	Group V Mean ± SD	
1.	Age (years)	35.10 ± 9.26	37.65 ± 11.60	0.447
2.	Height (cm)	166.50 ± 4.72	166.30 ± 4.66	0.893
3.	Weight (kg)	62.25 ± 6.41	62.80 ± 8.46	0.818
4.	Duration of surgery (hours)	2.15 ± 0.09	2.15 ± 0.08	0.913

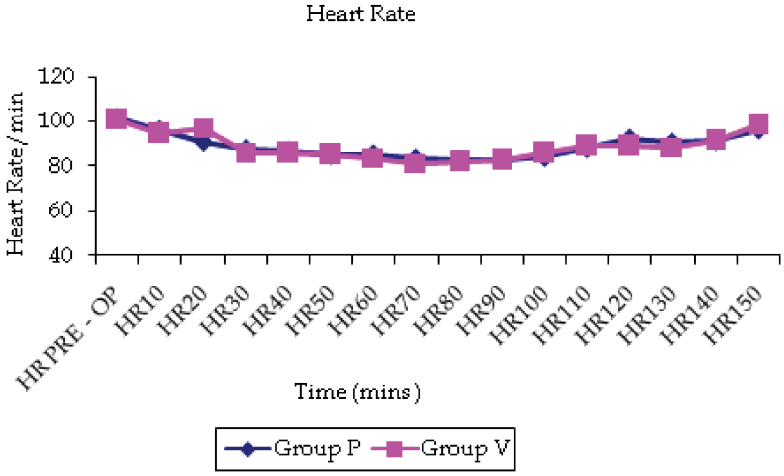

Fig. 1: Intraoperative Heart Rate Changes

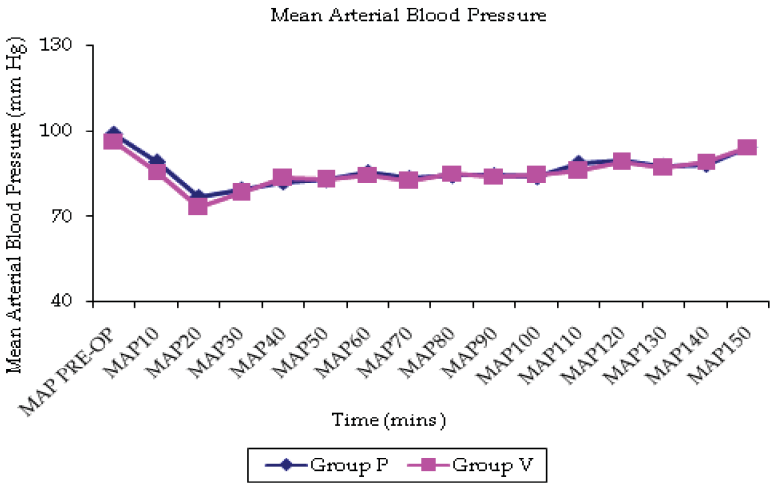

Fig. 2: Intraoperative Mean Arterial Pressure Changes

Table 2: Pain Score (Verbal Rating Scale)

S. No.	Parameters	Group		*p* value
		Group P Mean ± SD	Group V Mean ± SD	
1.	PS2 (hrs)	2.75 ± 0.44	0.00 ± 0.00	0.001**
2.	PS6 (hrs)	2.00 ± 0.46	0.45 ± 0.69	0.001**
3.	PS12 (hrs)	2.15 ± 0.49	1.70 ± 0.57	0.011*
4.	PS24 (hrs)	1.95 ± 0.69	1.60 ± 0.60	0.094
5.	PS48 (hrs)	1.85 ± 0.49	0.90 ± 0.31	0.001**

* $p < 0.05$ ** $p < 0.01$

Table 3: TFA and Total Postoperative Analgesic Requirements

S. No.	Parameters	Group		*p* value
		Group P Mean ± SD	Group V Mean ± SD	
1.	Time of First rescue analgesic (hr)	3.84 ± 0.46	6.42 ± 0.63	0.001**
2.	No. of supplementary analgesic doses (48 hr)	6.35± 0.49	4.25± 0.44	0.001**

* $p < 0.05$ ** $p < 0.01$

The study demonstrated that pain relief was significantly good ($p < 0.05$) in patients who received epidural bupivacaine with verapamil mixture than the patients who received epidural bupivacaine with placebo. Similar results were seen in time required for first analgesia and number of supplementary analgesic doses as summarized Table 3.

Discussion

Our knowledge of acute pain mechanisms has advanced sufficiently over the past decade so that rational rather than empirically derived therapy can be used by aiming specifically at interrupting the mechanisms responsible for the generation of clinical pain. Breakthrough pain after surgical procedures is now beginning to be recognized as constituting suboptimal management. This is an active research area. A number of clinical trials have been conducted to prove the efficacy of anti-nociceptive effect of Ca^{2+} channel blockers using different techniques and different types of drugs with conflicting results.[5,6,8,10]

The altered sensory processing caused by high-intensity noxious stimuli has several possible mechanisms, including an expansion of receptive fields and a decrease in thresholds of dorsal horn neurons; an enhancement of responses of dorsal horn neurons elicited by repetitive C fiber stimuli, which is known as wind-up phenomenon; and an increase in dynorphine gene expression6. Repetitive fast - transmitter activity of aspartate

and glutamate at α-amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid (AMPA)/ kinate receptors produces a membrane depolarization that counters a voltage-dependent blockade of the NMDA receptor by Mg^{2+}. Activation of neurokinin-1 receptors by substance P produces a slow, prolonged depolarization and enhances the influx of extracellular Ca^{2+} through voltage — operated Ca2+ channels. A further action of aspartate and glutamate on NMDA and metabotropic receptors produces an influx of Ca^{2+} through NMDA receptor-operated Ca^{2+} channels and activates phospholipase C.[7]

Phospholipase C catalyzes the formation of intracellular second messengers, which causes the release of Ca^{2+} from the endoplasmic reticulum. Increase in intracellular Ca^{2+} produced by these reactions results in increased gene expression and central sensitization, including wind-up and long-term potentiation.[3] Thus, calcium channel conductance is required for the nervous system to signal a painful situation. A disruption of calcium ion movement interferes with sensory processing and contributes to antinociception.[7]

This series of reactions may be prevented or attenuated either presynaptically by reducing the release of neurotransmitters, postsynaptically by blocking specific receptors, such as NMDA receptor, or by both mechanisms. Opioids and local anesthetics reduce the presynaptic release of the neurotransmitters.

Calcium channel blockers have antinociceptive effects in animals and show morphine potentiation in patients with chronic pain.[3,9] Substances with calcium channel-blocking effects and NMDA receptor antagonists may prevent pain and facilitate treatment of established pain states. In this study, we found that bupivacaine and verapamil administered epidurally, reduced the amount of analgesic that patients required postoperatively suggesting that verapamil may prevent central sensitization by surgical trauma.

In this double-blind study, we have evaluated the analgesic efficacy of bupivacaine with verapamil mixture given through lumbar epidural route in patient undergoing elective orthopedic lower limb surgeries.

Pain intensity was assessed using the verbal rating scale (VRS). Significant lower VRS scores after 2, 6, 12, 24 and 48 hours has demonstrated the clinical advantage of administering a single dose mixture of bupivacaine and verapamil through lumbar epidural route for effective postoperative analgesia.

Duration of analgesia was significantly more in Group V patients receiving bupivacaine and verapamil mixture (6.42 ± 0.63 hours) as compared to Group P (3.84 ± 0.46 hours). The demand for supplementary analgesic doses over 48 hours postoperatively was significantly low in Group V (4.25 ± 0.44 doses) than Group P (6.35 ± 0.49 doses).

Bradycardia with a heart rate < 60/ min was not encountered in any of the patient in both the groups.

Two patients of placebo group (10% of Group P) and one patient of verapamil group (5% of Group V) had episodes of hypotension with a MAP < 65 mm Hg during intraoperative period who were managed with a single dose of ephedrine 6 mg IV and crystalloids.

Postoperatively two patients of placebo group (10% of Group P) and one patient of verapamil group (5% of Group V) had episodes of hypotension with a MAP < 65 mm Hg. These patients were found to have an excessive blood loss seen in the operative wound drain, who are managed with compatible whole blood transfusion. No incidence of any bradycardia was noted in both the groups during postoperative period.

References

1. Miranda HF, Bustamante D, Kramer V, *et al.* Antinociceptive effects of Ca^{2+} channel blockers. Eur J Pharmacol. 1992;217:137–41. [PubMed].
2. Reves JG, Kissin I, Lell WA, *et al.* Calcium entry blockers: Uses and implications for anesthesiologists. Anesthesiology. 1982;57:504–18. [PubMed].
3. Hara K, Saito Y, Kirihara Y, *et al.* Antinociceptive effects of intrathecal L-type calcium channel blockers on visceral and somatic stimuli in the rat. Anesth Analg. 1998;87:382–7.[PubMed].
4. Omote K, Iwasaki H, Kawamata M,*et al.* Effects of verapamil on spinal anesthesia with local anesthetics. Anesth Analg. 1995;80:444–48.
5. Reuben SS, Reuben JB. Brachial plexus anesthesia with verapamil and/or morphine. Anesthesia Analgesia. 2000 Aug;9(2):379–83.
6. Brose WG, Gutlove DP, Luther RR, *et al.* Use of intrathecal SNX-111, a novel, N-type, voltage-sensitive, calcium channel blocker, in the management of intractable brachial plexus avulsion pain. Clin J Pain. 1997;13:256–9.
7. Pirec V, Laurito CE, Lu Y, *et al.* The combined effects of N-type calcium channel blockers and morphine on A delta versus C fiber mediated nociception. Anesth Analg. 2001;92:239–43. [PubMed]

8. Laurito CE, Cohn SJ, Becker GL. Effects of subcutaneous verapamil on the duration of local anesthetic blockade. J Clin Anesth. 1994;6:414–8. [PubMed]
9. Hasegawa AE, Zacny JP. The influence of three L-type calcium channel blockers on morphine effects in healthy volunteers. Anesth Analg. 1997;85:633–8. [PubMed]
10. Del Pozo E, Ruiz-García C, Baeyens JM. Analgesic effects of diltiazem and verapamil after central and peripheral administration in the hot-plate test. Gen Pharmacol 1990;21:681–5. [PubMed]